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1,2,4-TRIAZOLO[1,5-*a*][1,3,5]TRIAZINES (5-AZAPURINES): SYNTHESIS AND BIOLOGICAL ACTIVITY

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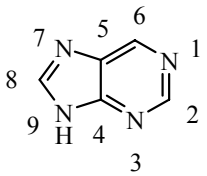
Abstract – The present review gives an account of the various synthetic routes to the 5-aza-analogue of purine-1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus and polyfused systems bearing this heterocyclic core. Data concerning biological activity of the compounds with 1,2,4-triazolo[1,5-*a*][1,3,5]triazine skeleton are also discussed.

Dedicated to Professor Viktor E. Kolla on the occasion of his 80th birthday

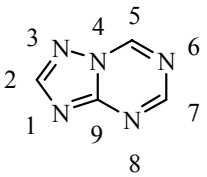
CONTENTS

1. INTRODUCTION

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazine heterocyclic system may be considered as a purine that has its carbon atom at C5 replaced by a nitrogen atom, henceforth it is called 5-azapurine (Figure 1). This close structural resemblance of 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus to purine allows compounds that have this scaffold to interfere with the effects of the biological purines (*i.e.* adenosine, guanine and xanthine). The derivatives of 5-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine, for instance, have been found to be one of the most effective and selective class of adenosine receptor inhibitors. The metabolism of xanthine may be affected by the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine derivatives through the inhibition of the enzyme xanthine oxidase (dehydrogenase). The diversity in biological activity of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazines is being discussed in more detail in the section 6 of this review.



purine



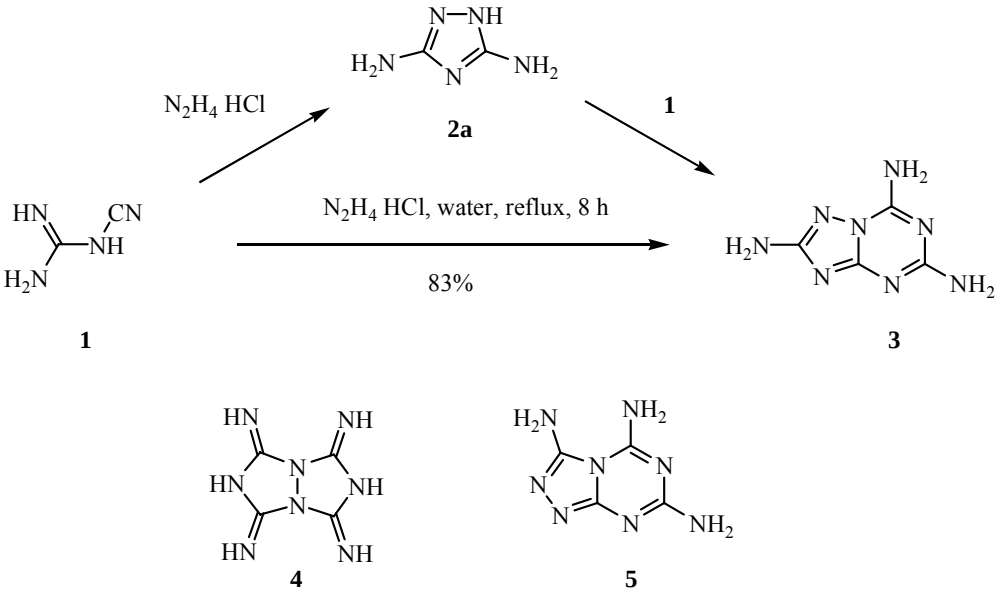
1,2,4-triazolo[1,5-*a*][1,3,5]triazine

(5-azapurine)

Figure 1

The synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazine derivative was first described by Pellizzari and Roncaglilo in 1901.[1] However, the real structure of the compound they obtained was established only recently. It was found that 3,5-diamino-1,2,4-triazole (guanazole, **2a**), a product from the reaction of cyanoguanidine (**1**) and hydrazine hydrochloride, could react further with another molecule of **1** to give 2,5,7-triamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**3**) (Scheme 1). The same compound (**3**) could be also

obtained directly using hydrazine hydrochloride and two equivalents of **1**. Pellizzari and Roncagliolo named the product of the reaction as guanazoguanazole and assigned structure (**4**) to it;[1] later in 1953, the structure of the product was improperly revised to be 1,2,4-triazolo[4,3-*a*][1,3,5]triazine (**5**).[2] It was only in the year 2000, that the [1,5-*a*] ring junction structure of **3** was established unambiguously using X-Ray crystallography.[3]



Scheme 1

Today, there are several common approaches available for the synthesis of 1,2,4-triazolo-[1,5-*a*][1,3,5]triazine and they may be categorized into: (A) annulation of the 1,3,5-triazine ring onto a 1,2,4-triazole scaffold; (B) annulation of the 1,2,4-triazole ring onto a 1,3,5-triazine scaffold; (C) concurrent formation of both the 1,3,5-triazine and 1,2,4-triazole rings; (D) syntheses *via* ring transformation reactions.

2. SYNTHESIS BY ANNULATION OF THE 1,3,5-TRIAZINE RING ONTO A 1,2,4-TRIAZOLE SCAFFOLD

The synthetic approaches based on 1,3,5-triazine ring annulation are diverse and have found wide and versatile applications. Suitably functionalized 1,2,4-triazoles can be cyclized to 1,2,4-triazolo-[1,5-*a*][1,3,5]triazines according to the following schematically represented plan (Scheme 2):

2.1. Two-bond formation through (3+3) atoms heterocyclization of 3(5)-amino-1,2,4-triazoles with reagents introducing C-N-C fragment.

2.2. Two-bond formation through (4+2) atoms heterocyclization of 1,2,4-triazoles having –N-C appendage at C3(5) with reagents introducing N-C fragment.

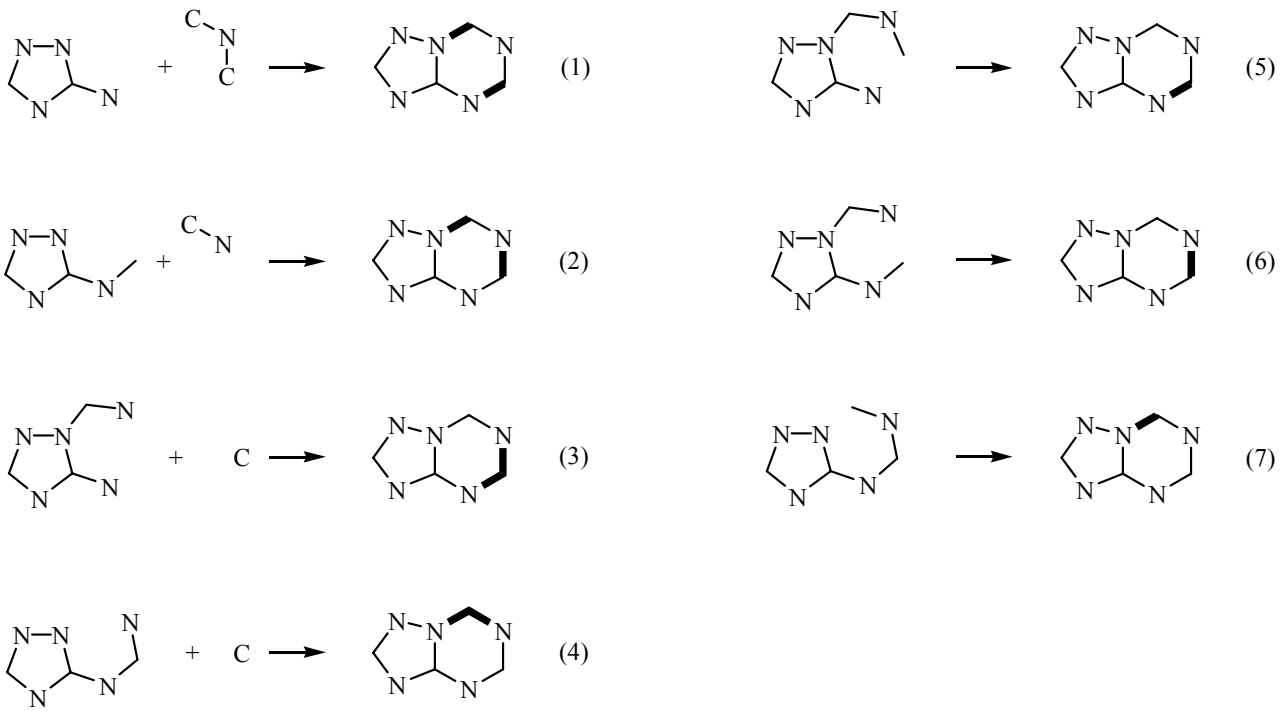
2.3. Two-bond formation through (5+1) atoms heterocyclization of 5-amino-1,2,4-triazoles having –C-N appendage at N1 with one carbon atom.

2.4. Two-bond formation through (5+1) atoms heterocyclization of 1,2,4-triazoles having –N-C-N appendage at C3(5) with one carbon atom.

2.5. One bond formation through (6+0) atoms intramolecular heterocyclization of 5-amino-1,2,4-triazoles having –C-N-C appendage at N1.

2.6. One bond formation through (6+0) atoms intramolecular heterocyclization of 1,2,4-triazoles having –N-C appendage at C5 and –C-N appendage at N1.

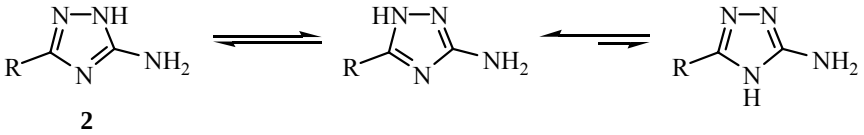
2.7. One bond formation through (6+0) atoms intramolecular heterocyclization of 1,2,4-triazoles having –N-C-N-C appendage at C3(5).



Scheme 2

2.1. Two-bond formation through (3+3) atoms heterocyclization of 3(5)-amino-1,2,4-triazoles with reagents introducing C-N-C fragment.

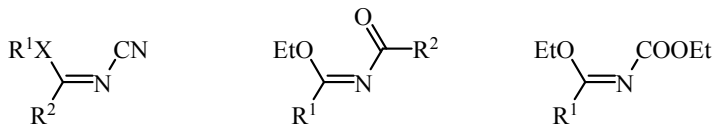
The large number of readily available 3(5)-amino-1,2,4-triazoles makes them popular choice for three-atom building blocks in the synthesis of fused heterocyclic systems that incorporate the 1,2,4-triazole ring as well as the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus. Because of annular prototropic tautomerism 3(5)-amino-1,2,4-triazoles (**2**) may theoretically exist in an equilibrium between three theoretically possible forms (Figure 2). The 4*H*-form was found to be disfavored, compounds (**2**) exist in 3- and 5-amino forms with the ratio that depends on the substituent R and external factors.[4] The tautomerism plays an important role in regioselectivity of the ring closure reactions and may result in the formation of the isomer mixtures.



2

Figure 2

The (3+3) heterocyclization of 3(5)-amino-1,2,4-triazoles (**2**) with reagents introducing C-N-C fragment is one of the most extensively explored group of the methods for the preparation of 1,2,4-triazolo-[1,5-*a*][1,3,5]triazines. Thus, the substituted imidates (*N*-cyano- (**6**), *N*-acyl- (**7**) and *N*-carbethoxy imidates (**8**)) are often used as this type of triatomic synthons (Figure 3).



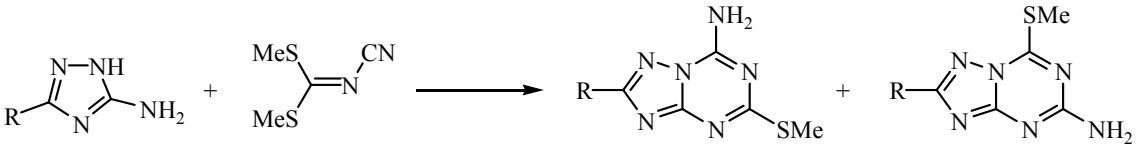
R^1X = MeS, PhO, EtO

6 **7** **8**

Figure 3

The reaction of 3(5)-amino-1,2,4-triazoles (**2**) with dimethyl *N*-cyanodithiocarbonimidate (**6a**, $R^1X = R^2$ = SMe) was described in several reports[5-12] (Scheme 3). Different reaction conditions (Table 1) were used and isomeric products (**9**) and (or) (**10**) were isolated. The ratio of the formed products depended on the type of the substituent R at the aminotriazole (**2**) and the reaction conditions. This reaction was used for the preparation of 7-amino-2-furyl-5-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**9c**) which became a key starting material in the syntheses of adenosine receptors inhibitors (*vide infra*). When the reaction was carried out at high temperature (170-180 ºC) under argon, a separable mixture of the isomers (**9c**) and (**10c**) was obtained.[7,8] The reaction that used an anion, preformed from aminotriazole (**2**) after treatment with sodium hydride, at temperature below 0 ºC afforded the isomer (**10c**) exclusively.[7] The compound (**9b**) obtained from this type of reaction was also an important intermediate for the synthesis of a biologically active sulphone.[6]

The phenoxy group of more reactive diphenyl *N*-cyanocarbonimidate (**6b**, $R^1X = R^2$ = OPh) was found to react with amino group of **2** with greater regioselectivity (Scheme 4).[7] However, it was observed that under the mild reaction conditions the cyano group might attack N1 as well as N4 with a ring closure leading to the formation of **11** and **12**. The thermodynamically less stable 1,2,4-triazolo[4,3-*a*][1,3,5]triazine (**12**) was capable of rearranging to 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**11**) upon heating or in the presence of catalytic amount of base. Performing the reaction in refluxing solvents led to the isolation of **11** exclusively suggesting the occurrence of a spontaneous rearrangement. Further examples of this type of rearrangement are listed in Section 5.1 of this review. Considerable amount of polymeric material was also formed in the reactions of 3(5)-amino-1,2,4-triazoles (**2**) with **6b**. The structures of the synthesized compounds were confirmed with spectral data and X-Ray crystallographic study of **11a**.



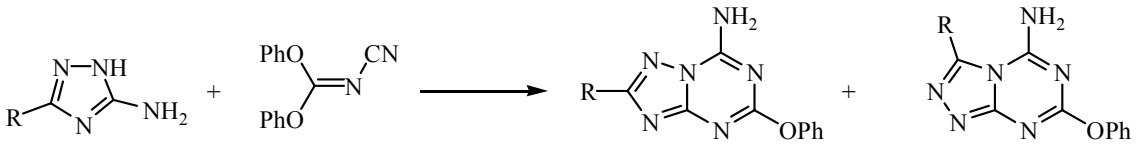
2 **6a** **9** **10**

Scheme 3

Table 1. Reactions of 3(5)-amino-1,2,4-triazoles (**2**) with dimethyl *N*-cyanodithiocarbonimidate (**6a**).

Compd.	R	Reaction conditions	Yield, %	Refs.
9a	H	Py, reflux, 2.5 h	20	5
10a	H	Py, 50 ºC, 36h	8.4	5
9b	C_6H_4Me-3	180 ºC, 1 h	23	6
9c	2-Furyl	170 ºC, argon, 1 h	20	8-12
9c+10c	2-Furyl	170 ºC, argon, 1 h	18+9*	8
9c+10c	2-Furyl	180 ºC, argon, 1 h	35+7*	7
10c	2-Furyl	< 0 ºC, NaH, DMF, 3 h	20	7
9d+10d	OPh	140 ºC, argon, 1 h	14+20	7

* - Yields of components after separation



2 **6b** **11** **12**

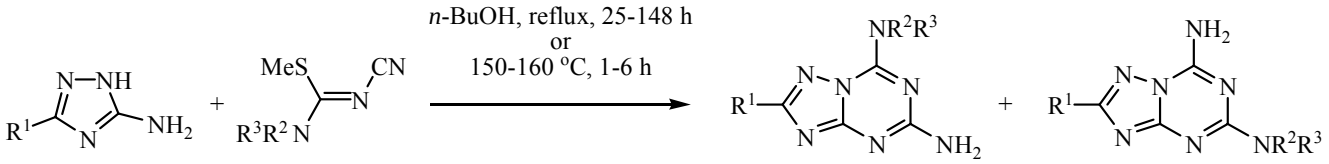
Scheme 4

Table 2. Reactions of 3(5)-amino-1,2,4-triazoles (**2**) with diphenyl *N*-cyanodicarbonimidate (**6b**).[7]

Compd.	R	Reaction conditions	Yield, %
11a+12a	2-Furyl	MeCN, rt, 3 days	12.5+12*
11b	SMe	DME, reflux, 3 h	16
12b	SMe	DME, rt, 3 h	18

* - Yields of components after separation

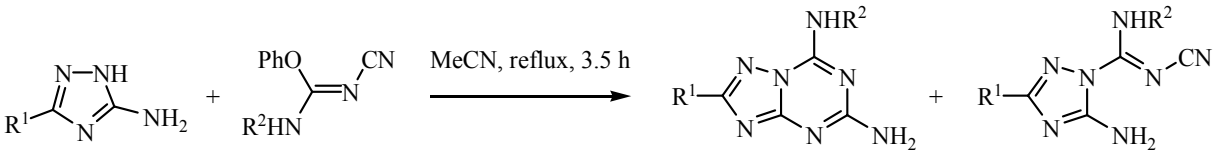
Caulkett et al. reported[7] that reaction of **2** (R = Furyl) with *N*-substituted *N'*-cyano-*S*-methylisothioureas (**6c**) did not proceed at temperature below 200 ºC and decomposition was observed at higher temperature. In further work[13] it was demonstrated that long time refluxing of the reagents (**2**) and (**6c**) in *n*-butanol afforded 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**13**) and a minor regioisomer (**14**) (Scheme 5). Similar results were obtained when reactions were carried out in melt at 150-160 ºC. In the series of the reactions, **13** were prepared in yield up to 69% whereas yield of **14** did not exceed 4%. The structures of the prepared compounds were established using ^{1}H and ^{13}C NMR spectral data and X-ray crystallographic study of **13** ($R^1 = NR^2R^3 = NHEt$).



2 **6c** **13** **14**

Scheme 5

When an amino derivative of diphenyl *N*-cyanocarbonimidate (**6d**) was allowed to react with 3(5)-amino-5(3)-furyl-1,2,4-triazole (**2**), an uncyclised *N*-cyano compound (**16**) was formed together with 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**15**) (Scheme 6).[7] The compound (**16**) was found to undergo (6+0) type of cyclisation in hot ethanolic ammonia to afford **15**. Other examples of this formal approach to 1,3,5-triazine ring annulation can be found in Section 2.5 of this review.

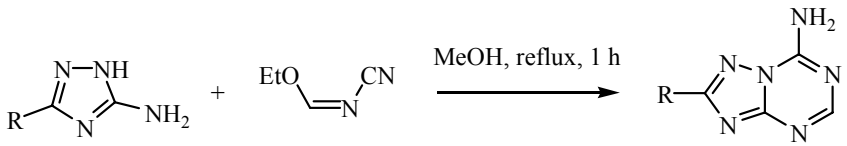


2 **6d** **15** **16**

R^1 = 2-Furyl, R^2 = $CH_2CH_2C_6H_4OH$-4, 27% (**15**) + 10% (**16**)

Scheme 6

It was reported[14] that 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**17**) may be prepared from 3(5)-amino-1,2,4-triazoles (**2**) upon treatment with ethyl *N*-cyanoformimidate (**6e**) (Scheme 7).

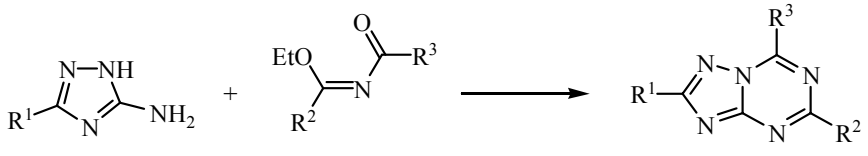


2 **6e** **17**

R = H, 93% (**17a**); Me, 70% (**17b**); Et, 66% (**17c**); Ph, 78% (**17d**)

Scheme 7

The reaction of 3(5)-amino-1,2,4-triazoles (**2**) with ethyl *N*-acylimidates (**7**) was used for the syntheses of substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**18**) (Scheme 8). When **2** was heated in ethanol with ethyl *N*-acylbenzoimidates (**7,** R^2 = Ph), 7-alkyl-5-phenyl substituted **18a,b,e** were obtained in 75% yield (Table 3).[15] 5,7-Diaryl substituted **18c,d,f,g** were prepared by melting of the reagents at 165-170 ºC.[16] For the synthesis of 2-chloro-*N*-(5,7-dimethyl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-2-yl)benzenesulfonamide (**18h**) possessing herbicidal activity, the cyclocondensation of the corresponding 3(5)-amino-1,2,4-triazoles (**2**) with ethyl *N*-acetylacetimidate (**7**, R^2 = R^3 = Me) was used.[17,18] This reaction was carried out in DMF and required heating at 60-70 ºC for a long time (Table 3).



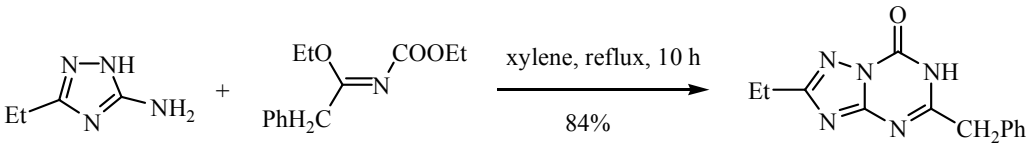
2 **7** **18**

Scheme 8

Table 3. Reactions of 3(5)-amino-1,2,4-triazoles (**2**) with ethyl *N*-acylimidates (**7**).

Compd.	R^1	R^2	R^3	Reaction conditions	Yield, %	Refs.
18a	H	Ph	Me	EtOH, reflux, 4 h	75	15
18b	H	Ph	*i*-Pr	EtOH, reflux, 4 h	75	15
18c	H	Ph	Ph	165-170 ºC, 2 h	76	16
18d	H	Ph	C_6H_4Me-4	165-170 ºC, 2 h	80	16
18e	Et	Ph	Me	EtOH, reflux, 4 h	75	15
18f	NH_2	Ph	Ph	165-170 ºC, 2 h	70	16
18g	NH_2	Ph	C_6H_4Me-4	165-170 ºC, 2 h	77	16
18h	$SO_2NHC_6H_4Cl$-2	Me	Me	DMF, 60-70 ºC, 40 h	53	18

The cyclization of 3(5)-amino-5(3)-ethyl-1,2,4-triazole with ethyl *N*-(carbethoxy)phenylacetimidate (**8**) was reported[15] to proceed in refluxing xylene yielding 84% of 7-oxo-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**19**) (Scheme 9).

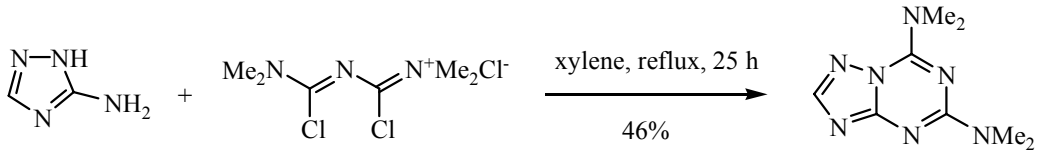


2 **8** **19**

Scheme 9

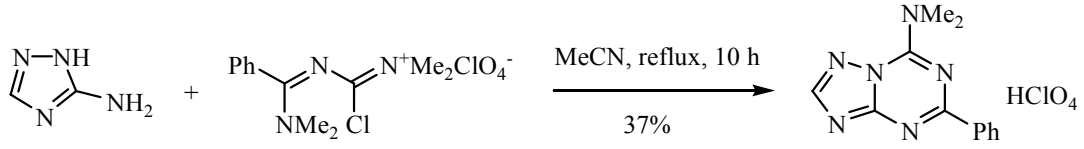
Besides the substituted imidates, a number of other electrophilic reagents may be used as triatomic synthons for the annulation of the 1,3,5-triazine ring to 3(5)-amino-1,2,4-triazoles. The reaction of 3(5)-amino-1,2,4-triazole (**2**) with azacyanine (**20**) in refluxing xylene was found to afford 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**21**) (Scheme 10).[19] The authors[19] proposed that the cyclization took place at position N4 and the compound (**21**) was formed after consecutive rearrangement of the intermediate with [4,3-*a*] ring junction. However, a confirmation of this pathway was not presented; and direct cyclization at position N1 of the triazole (**2**) appeared to be the more realistic route.

The reaction of 3(5)-amino-1,2,4-triazole (**2**) with diazaiminium perchlorate (**22**) was shown to give the 1,2,4-triazolo[1,5-*a*][1,3,5]triazinium perchlorate (**23**) (Scheme 11).[20] The salt (**23**) could be treated with 10% sodium hydroxide to release the corresponding free base in 77% yield.[21]



2 **20** **21**

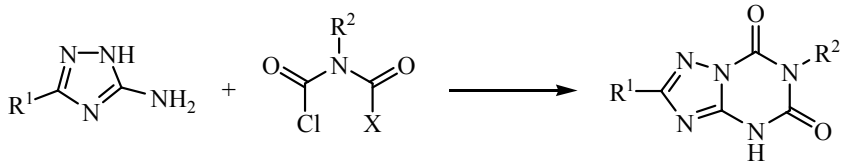
Scheme 10



2 **22** **23**

Scheme 11

The 5,7-dioxo-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**25**) were synthesized from 3(5)-amino-1,2,4-triazoles (**2**) *via* cyclization with **24** (Scheme 12).[22]

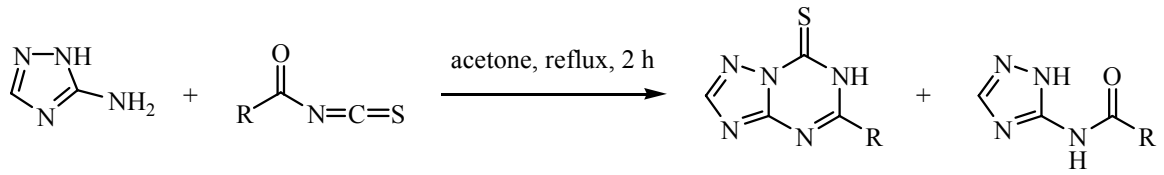


2 **24** **25**

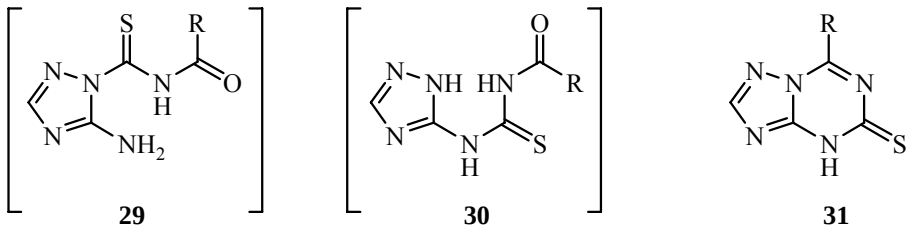
X = Cl, OEt

Scheme 12

It was reported[23] that 7-thioxo substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**27**) were formed as one of the products from the reaction of **2** with *N*-aroyl isothiocyanates (**26**) in refluxing acetone (Scheme 13).



2 **26** **27** **28**



29 **30** **31**

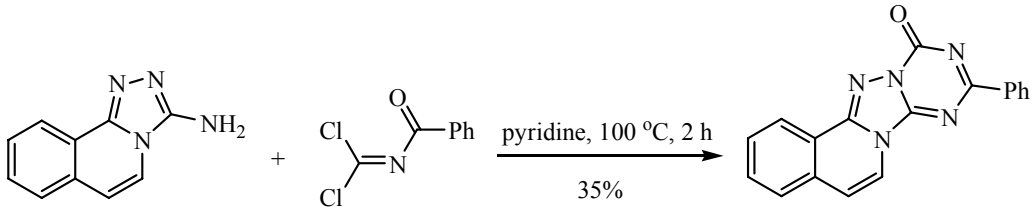
R = Ph, 28% (**27a**) + 49% (**28a**); C_6H_4Cl-4, 22% (**27b**) + 52% (**28b**)

Scheme 13

In this reaction, the formation of an intermediate (**29**) after initial attack of the endocyclic nitrogen N1 with **26** was proposed. However, isothiocyanates were shown to react on heating with exocyclic nitrogen of

3(5)-amino-1,2,4-triazoles (**2**).[24-26] Therefore, an alternative pathway of the reaction *via* intermediate (**30**) and formation of isomeric 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**31**) can not be excluded.

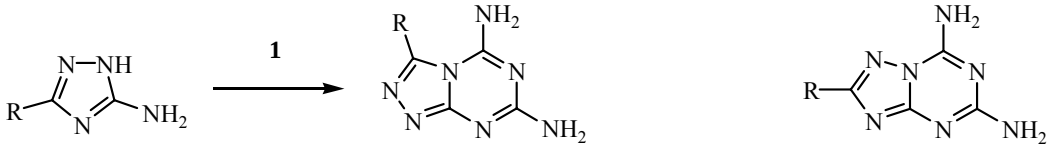
The preparation of the tetracyclic system with 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus (**34**) in 35% yield was reported[27] from the corresponding amino-1,2,4-triazole derivative (**32**) and *N*-(dichloromethylene)benzamide (**33**) (Scheme 14).



32 **33** **34**

Scheme 14

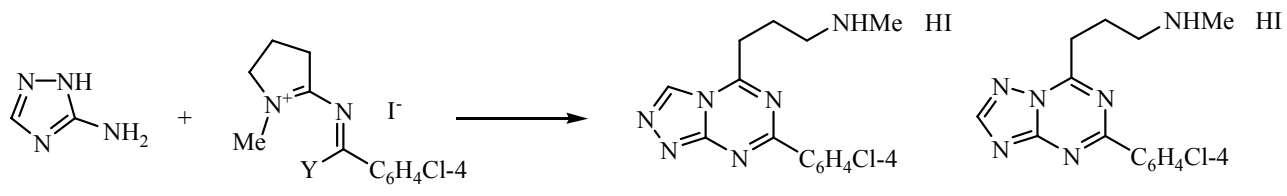
Apropos of the reactions of 3(5)-amino-1,2,4-triazoles (**2**) with cyanoguanidine (**1**), several reports[2,28,29] assigned 1,2,4-triazolo[4,3-*a*][1,3,5]triazine structure (**35**) to the products obtained (Scheme 15), but there was no univocal evidence of the involvement of the triazole N4 atom in the reaction. Therefore, 1,2,4-triazolo[1,5-*a*][1,3,5]triazine structure (**36**) could not be excluded for the synthesized compounds (*cf.* Scheme 1). Based on the recent report[3] on the X-ray structure evaluation of the related compound (**3**) we conclude that further structure verification is required for the products of these reactions.



2 **35** **36**

Scheme 15

In view of the fact that annulation of the 1,3,5-triazine ring to 3(5)-amino-1,2,4-triazoles as a rule leads to the fused system with [1,5-*a*] ring junction, the reaction of 3(5)-amino-1,2,4-triazole (**2**) with **37** might result in the formation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**39**) rather than the reported[30] compound (**38**) (Scheme 16).

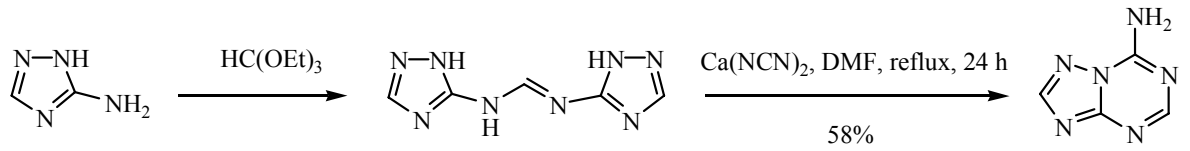


2 **37** **38** **39**

Scheme 16

2.2. Two-bond formation through (4+2) atoms heterocyclization of 1,2,4-triazoles having –N-C appendage at C3(5) with reagents introducing N-C fragment.

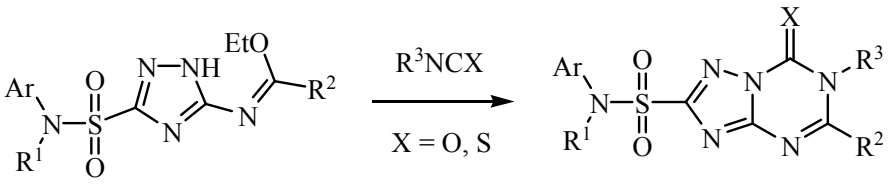
The reaction of the *N*,*N'*-disubstituted formamidine (**40**) with calcium cyanamide represents an example of [4+2] heterocyclization in the synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (Scheme 17). Heating of the reagents in DMF under reflux for 24 h afforded 7-amino[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (5-azaadenine, **17a**) in 58% yield.[31]



2 **40** **17a**

Scheme 17

When the iminoesters (**41**) were allowed to react with iso(thio)cyanates, 7-(thi)oxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**42**) possessing herbicidal activity were formed (Scheme 18).[32] It should be noted that reaction of the iminoesters derived from 3(5)-amino-1,2,4-triazole with iso(thio)cyanates was reported to give the fused system with [4,3-*a*] ring junction.[33] However, no detail information on the regioselectivity of this type of reactions was reported.

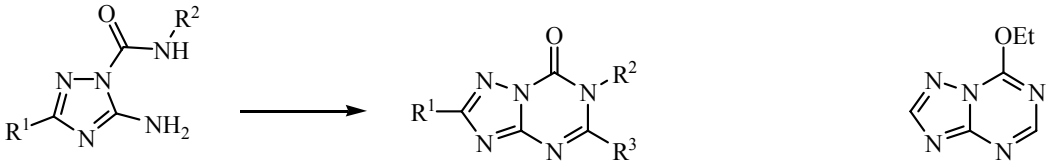


41 **42**

Scheme 18

2.3. Two-bond formation through (5+1) atoms heterocyclization of 5-amino-1,2,4-triazoles having –C-N appendage at N1 with one carbon atom.

The reactions of 5-amino-1,2,4-triazoles with –C-N appendage (*i.e.* carboxamidic, carbothioamidic or guanyl fragment) at N1 with one-carbon inserting cyclizing reagents (triethyl orthoesters, diethoxymethyl acetate, formic acid, ethyl chloroformate) were described. The heating of 5-amino-1,2,4-triazole-1-carboxamides (**43**) with triethyl orthoformate or diethoxymethyl acetate gave 7-oxo[1,2,4]triazolo-[1,5-*a*][1,3,5]triazines (**44**) (Scheme 19, Table 4). It should be noted that more intensive heating (140 ºC) of 5-amino-1,2,4-triazole-1-carboxamide (**43**, R^1 = R^2 = H) in triethyl orthoformate afforded 7-ethoxy[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**45**) in 60% yield.[5] Using of triethyl orthobenzoate as a cyclizing reagent led to the 5-phenyl substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**44b**).



43 **44** **45**

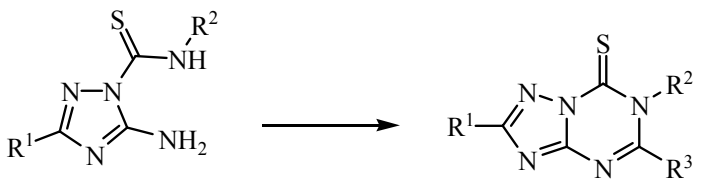
Scheme 19

Table 4. Synthesis of 7-oxo-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**44**) from 5-amino-1,2,4-triazole-1-carboxamides (**43**).

Compd.	R^1	R^2	R^3	Reagents and reaction conditions	Yield, %	Refs.
44a	H	H	H	$HC(OEt)_3$, 100 ºC, 18 h	62	31
				$HC(OEt)_3$, 100 ºC, 18 h	75	34
				$AcOCH(OEt)_2$, 100 ºC, 2 h	57	5
44b	H	H	Ph	$PhC(OEt)_3$, AcOH, DMF, reflux, 72 h	33	35
44c	$PhCH_2$	*n*-Bu	H	$AcOCH(OEt)_2$,DMF, 120 ºC, 2 h	67	36
44d	$PhCH_2$	C_6H_4Me-4	H	$AcOCH(OEt)_2$,DMF, 120 ºC, 2 h	65	36
44e	Ph	H	H	$HC(OEt)_3$, reflux, 1.5 h	64	26

A number of 7-thioxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**47**) was prepared by treatment of 5-amino-1,2,4-triazole-1-carbothiamides (**46**) with triethyl orthoesters or diethoxymethyl acetate (Scheme 20) under different reaction conditions (Table 5). Some of the synthesized compounds showed interesting biological activity (*vide infra*).[5]

The hydrochloric salts of 1-guanyl substituted 5-amino-1,2,4-triazoles (**48**) upon boiling in formic acid afforded 7-amino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**17**) in good yields (Scheme 21).[39] Using in the analogous reactions, free bases (**49**) gave the products of cyclization only in case of 3-aryl substituted triazoles (**49**, R = Ph, C_6H_4OMe-4). It was noted that triethyl orthoformate was an effective cyclizing reagent in the reactions with the salts (**48**) but not the free bases (**49**). The authors[39] supposed that the reactions would proceed with acid catalysis. When 5-amino-1-guanyl-3-phenyl-1,2,4-triazole (**49**, R = Ph) was heated in xylene, 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**50**) was obtained in 71% yield.

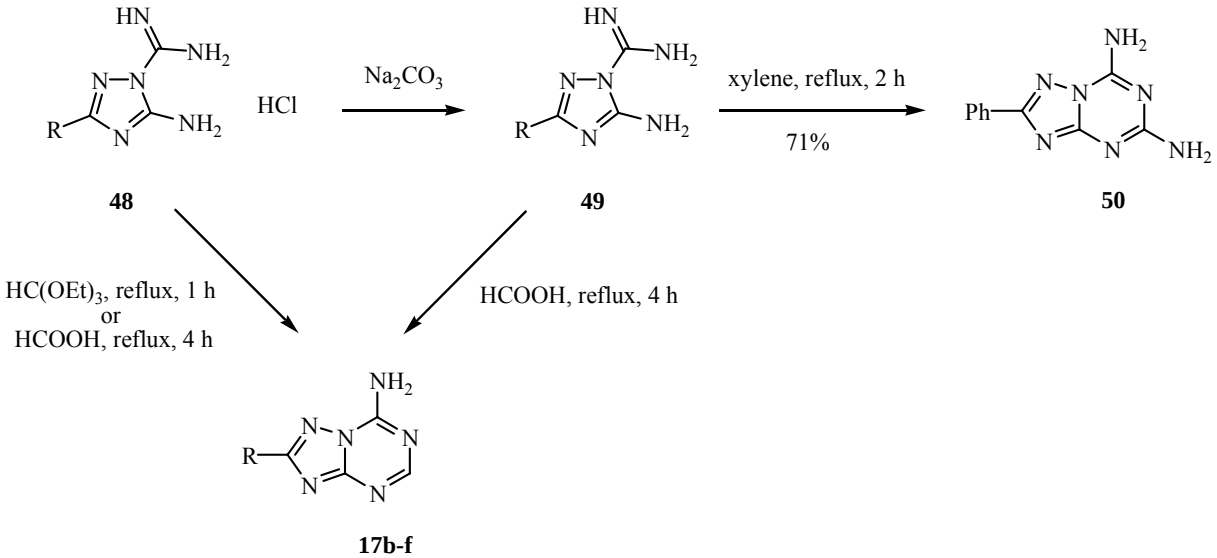


46 **47**

Scheme 20

Table 5. Synthesis of 7-thioxo-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**47**) from 5-amino-1,2,4-triazole-1-carbothioamides (**46**).

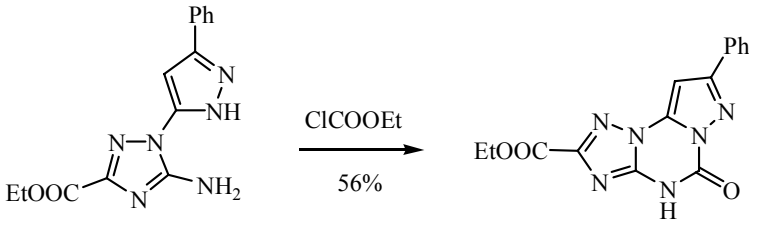
Compd.	R^1	R^2	R^3	Reagents and reaction conditions	Yield, %	Refs.
47a	H	Me	H	$AcOCH(OEt)_2$, rt, 20 h	88	34
				$AcOCH(OEt)_2$, 80 ºC, 2 h	88	5
47b	H	Me	Me	$MeC(OEt)_3$, 140 ºC, 3 h	22	5
47c	H	Me	Ph	$MeC(OEt)_3$, 140 ºC, 3 h	40	5
47d	H	*n*-Pro	H	$AcOCH(OEt)_2$, rt, 2 h	90	5
47e	H	*n*-Bu	H	$AcOCH(OEt)_2$, rt, 2 h	66	5
47f	Ph	Me	H	$AcOCH(OEt)_2$, rt, 2 h	92	5
47g	C_6H_4F-4	Me	H	$AcOCH(OEt)_2$, 90 ºC, 2 h	96	5
47h	C_6H_4Cl-4	Me	H	$AcOCH(OEt)_2$, 90 ºC, 2 h	96	5
47i	C_6H_4Cl-4	Me	Me	$MeC(OEt)_3$, AcOH, 140 ºC, 5 h	56	5
47j	C_6H_4Cl-4	Me	Ph	$PhC(OEt)_3$, 140 ºC, 3 h	59	5
47k	C_6H_4Br-4	Me	H	$AcOCH(OEt)_2$, 80 ºC, 2 h	97	5
47l	C_6H_4CN-4	Me	H	$AcOCH(OEt)_2$, 80 ºC, 2 h	90	5
47m	$C_6H_4CF_3$-4	Me	H	$AcOCH(OEt)_2$, 90 ºC, 2 h	93	5
47n	$C_6H_3Cl_2$-2,4	Me	H	$AcOCH(OEt)_2$, 80 ºC, 2 h	84	5
47o	$C_6H_3Cl_2$-3,4	Me	H	$AcOCH(OEt)_2$, 80 ºC, 2 h	80	5
47p	NHCOCOOEt	Me	H	$AcOCH(OEt)_2$, 90 ºC, 2 h	78	5
47q	SMe	Me	H	$HC(OEt)_3$, reflux, 3 h	72	37, 38
47r	SMe	Me	Me	$MeC(OEt)_3$, reflux, 3 h	59	37, 38
47s	SMe	Et	H	$HC(OEt)_3$, reflux, 3 h	48	37, 38
47t	SMe	Et	Me	$MeC(OEt)_3$, reflux, 3 h	50	37, 38
47u	SMe	*n*-Bu	Me	$MeC(OEt)_3$, reflux, 3 h	46	37, 38



R = Me, 85% (**17b**); Et, 75% (**17c**); Ph, 95% (**17d**); *n*-Pr, 80% (**17e**); C_6H_4OMe-4, 90% (**17f**)

Scheme 21

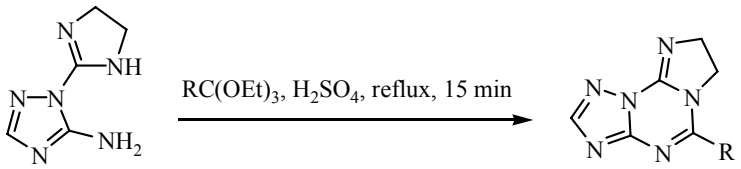
Several polycyclic compounds (**52**, **54** and **56**) bearing 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus were synthesized in the reactions of 5-amino-1-heteryl-1,2,4-triazoles (**51**, **53** and **55**) with ethyl chloroformate (Scheme 22)[40] or triethyl orthoesters of formic and acetic acid (Schemes 23 and 24).[41]



51 **52**

Scheme 22

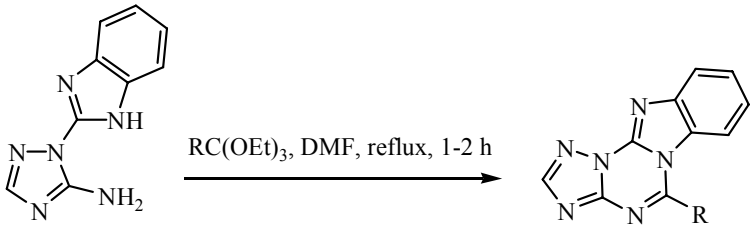
Using catalytic amount of sulfuric acid in the preparation of the tricyclic system (**54**) was found to facilitate the reaction. However, it was not effective for the synthesis of the tetracyclic compounds (**56**) due to the poor solubility of the starting aminotriazole (**55**) in the orthoesters.[41] The detail analysis of the ^{1}H and ^{13}C NMR spectra of the obtained heterocyclic systems (**54**) and (**56**) can be found in the paper.[42]



53 **54**

R = H, 59% (**54a**); Me, 47% (**54b**)

Scheme 23



55 **56**

R = H, 65% (**56a**); Me, 21% (**56b**)

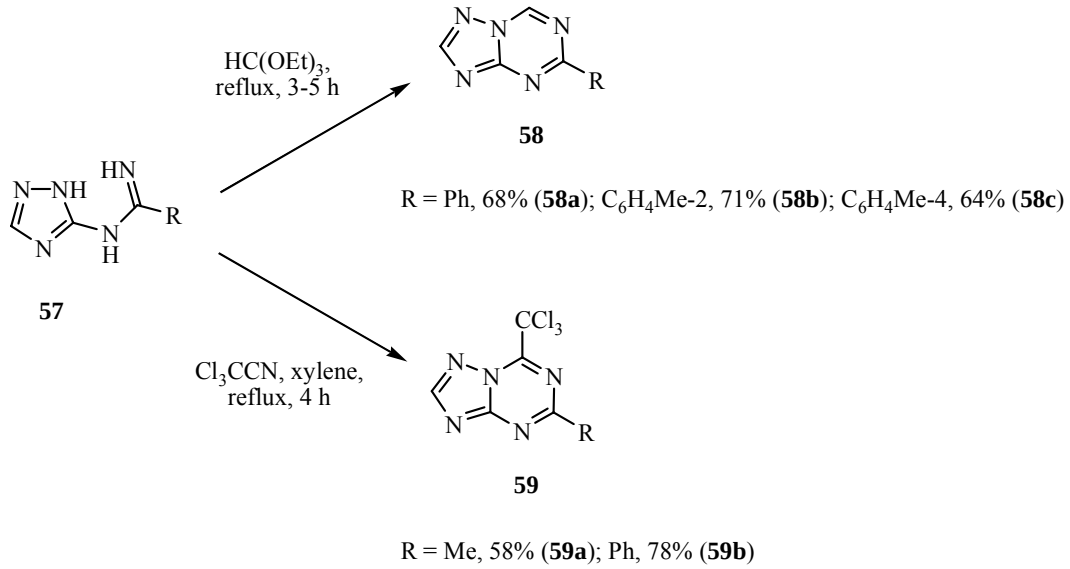
Scheme 24

2.4. Two-bond formation through (5+1) atoms heterocyclization of 1,2,4-triazoles having –N-C-N appendage at C3(5) with one carbon atom.

This type of heterocyclization realized in using as starting materials *N*-1,2,4-triazol-3(5)-yl substituted amidines, ureas, thioureas and guanidines. The nature of substituent at position 7 of the formed 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus would depend on the type of the one-carbon inserting synthon applied. The cyclization of *N*-(1,2,4-triazol-3(5)-yl)amidines (**57**) with triethyl orthoformate proceeded

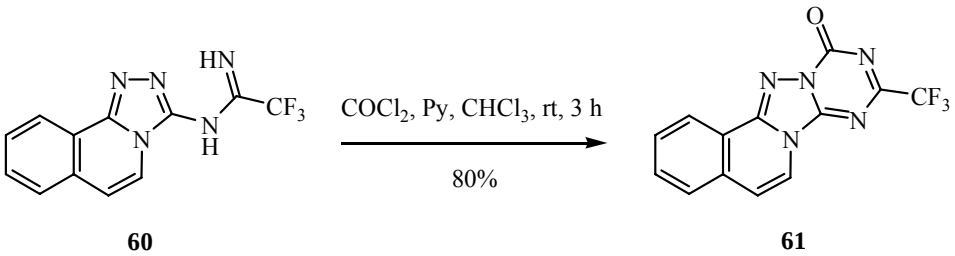
regioselectively and afforded 5-aryl-[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**58**) (Scheme 25).[43] The structure of the prepared compounds (**59**) was established based on spectral data. The results of ^{15}N NMR spectroscopy excluded the isomeric 1,2,4-triazolo[4,3-*a*][1,3,5]triazines. X-ray crystallographic study of 5-phenyl[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**58a**) synthesized according to the described method also confirmed the ring closure to N1 of the triazole (**57**).[44]

In a similar way, using trichloroacetonitrile as one-carbon cyclizing reagent in the reaction with the amidines (**57**), 7-trichloromethyl[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**59**) were obtained.[45] The structure of the compounds (**59**) was confirmed using spectroscopic methods including ^{15}N NMR spectroscopy.



Scheme 25

The synthesis of tetracyclic system (**61**) bearing 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus using the cyclization of the corresponding trifluoroacetylamidine (**60**) with phosgene (Scheme 26) was described.[46]

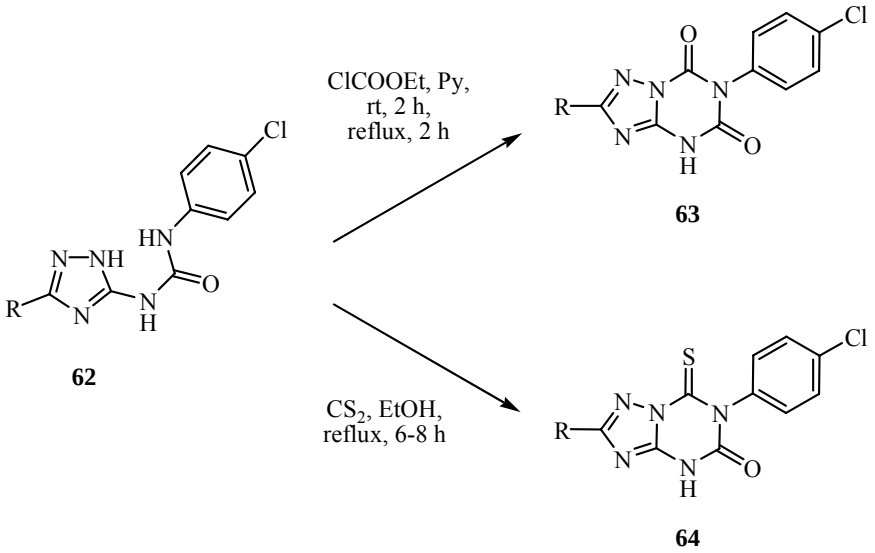


Scheme 26

The heterocyclizations of *N*-(1,2,4-triazol-3(5)-yl)-*N'*-(4-chlorphenyl)ureas (**62**) using ethyl chloroformate or carbon disulfide resulted in the formation of 5,7-dioxo or 5-oxo-7-thioxo substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**63**)[47] and (**64**),[48] respectively (Scheme 27).

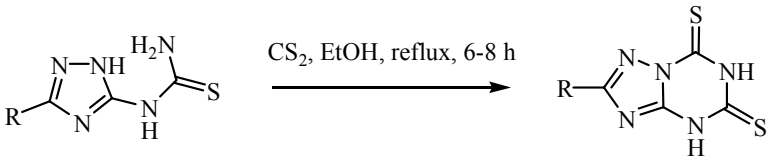
Analogously, *N*-(1,2,4-triazol-3(5)-yl)thioureas (**65**) were treated with carbon disulfide to afford 2-aryl-5,7-dithioxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**66**) (Scheme 28).[49]

It was reported that heating of *S*-substituted *N*-(1,2,4-triazol-3(5)-yl)isothioureas (**67**) in orthoesters led to the formation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**68**) (Scheme 29, Table 6).[24]



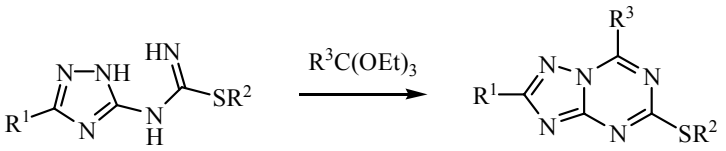
62 **63** **64**

Scheme 27



65 **66**

Scheme 28



67 **68**

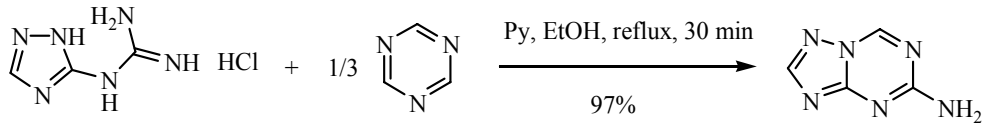
Scheme 29

Table 6. Reactions of *S*-substituted *N*-(1,2,4-triazol-3(5)-yl)isothioureas (**67**) with orthoesters.

Compd.	R^1	R^2	R^3	Reaction conditions	Yield, %	Refs.
68a	H	Me	Me	100 ºC, 2.5 h	nr	24
68b	H	Me	Et	100 ºC, 2.5 h	39	24
68c	Me	Me	H	reflux, 1 h	53	50
68d	Me	Me	Me	100 ºC, 2.5 h	nr	24
68e	Me	Me	Et	100 ºC, 2.5 h	nr	24
68f	Me	CH_2Ph	H	reflux, 1 h	61	50
68g	Et	Me	Me	100 ºC, 2.5 h	nr	24
68h	Et	Me	Et	100 ºC, 2.5 h	nr	24
68i	Ph	Me	H	reflux, 1 h	82	50
68j	Ph	Me	Me	100 ºC, 2.5 h	nr	24
68k	Ph	Me	Et	100 ºC, 2.5 h	nr	24
68l	Ph	CH_2Ph	H	reflux, 1 h	81	50
68m	Ph	$C_6H_4NO_2$-4	H	reflux, 1 h	62	50

nr – not reported

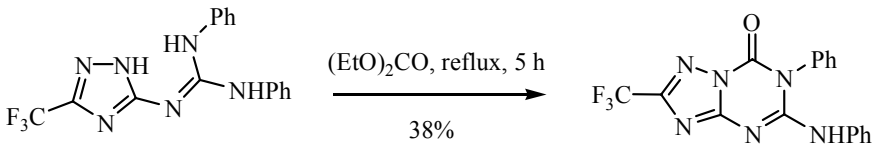
The use of *s*-triazine as a condensing agent in the reaction with *N*-(1,2,4-triazol-3(5)-yl)guanidine (**69**) made enable to prepare 5-amino[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**70**) in excellent yield (Scheme 30).[51]



69 **70**

Scheme 30

The ring closure carbonylation of *N',N''*-diphenyl derivative of *N*-(1,2,4-triazol-3(5)-yl)guanidine (**71**) using diethyl carbonate afforded the formation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**72**) (Scheme 31).[52]

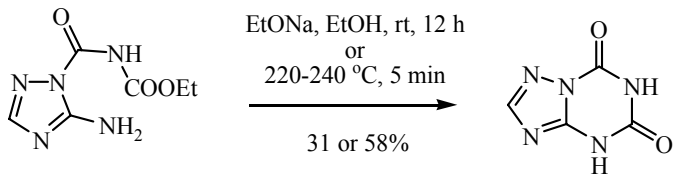


71 **72**

Scheme 31

2.5. One-bond formation through (6+0) atoms intramolecular heterocyclization of 5-amino-1,2,4-triazoles having –C-N-C appendage at N1.

This type of reactions may be exemplified by intramolecular heterocyclization of 5-amino-1-carbethoxy(thio)carbamoyl-1,2,4-triazoles leading to 5-oxo-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]-triazine. Thus, it was found that 5-amino-1-carbethoxycarbamoyl-1,2,4-triazole (**73**) in alkaline medium or in the result of pyrolysis underwent cyclization with the formation of 5,7-dioxo[1,2,4]-triazolo[1,5-*a*][1,3,5]triazine (5-azaxanthine, **74**) (Scheme 32).[53]



73 **74**

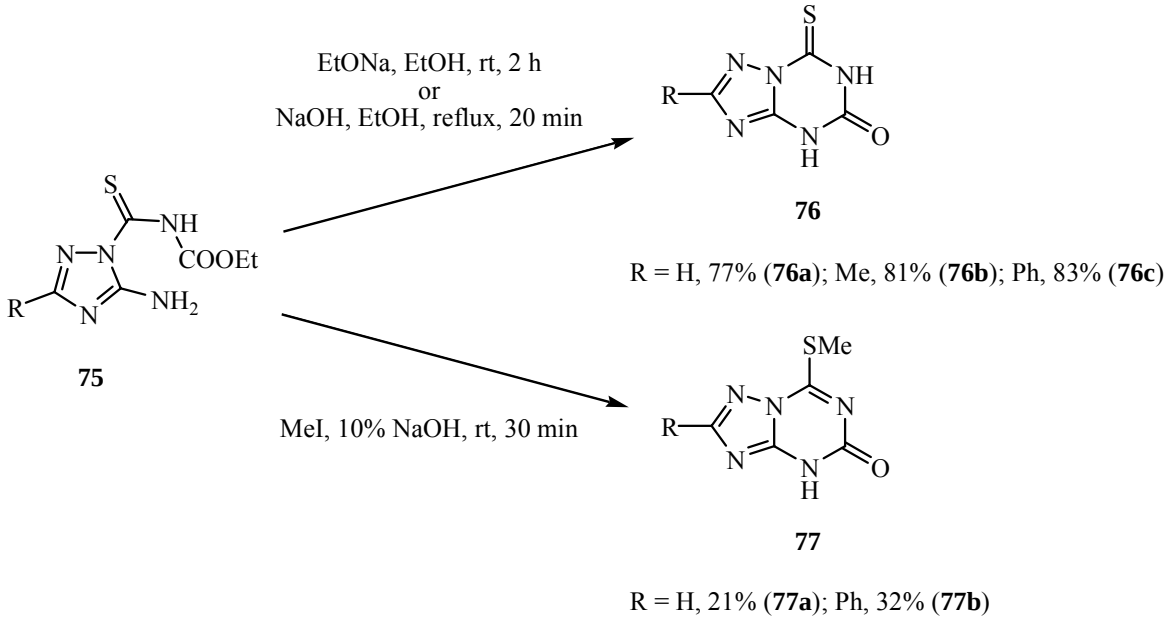
Scheme 32

In a similar way, 5-amino-1-carbethoxylthiocarbamoyl-1,2,4-triazole (**75**) in alkaline medium cyclized to 5-oxo-7-thioxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**76**).[26,34] The corresponding 7-methylthio derivatives (**77**) were prepared by treatment of **75** with iodomethane in aqueous alkali (Scheme 32).[26]

2.6. One-bond formation through (6+0) atoms intramolecular heterocyclization of 1,2,4-triazoles having –N-C appendage at C5 and –C-N appendage at N1.

The example of this type of heterocylization has more theoretical rather than practical importance. It was found that ring closure of the triazole (**78**) in either *p*-tosyl chloride – pyridine mixture or in sodium

acetate – acetic anhydride solution afforded 6,7-dihydro-6-methyl-7-thioxo[1,2,4]triazolo[1,5-*a*][1,3,5]-triazine (**47a**) (Scheme 34) but yields were low.[34]



75

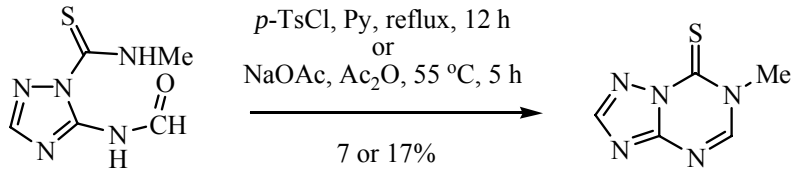
76

R = H, 77% (**76a**); Me, 81% (**76b**); Ph, 83% (**76c**)

77

R = H, 21% (**77a**); Ph, 32% (**77b**)

Scheme 33

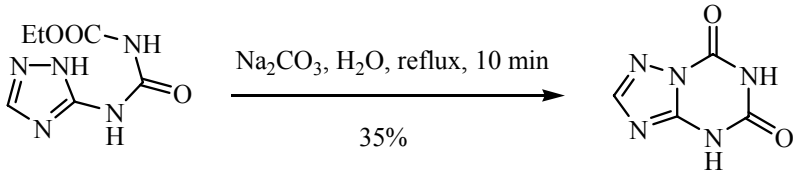


78 **47a**

Scheme 34

2.7. One-bond formation through (6+0) atoms intramolecular heterocyclization of 1,2,4-triazoles having –N-C-N-C appendage at C3(5).

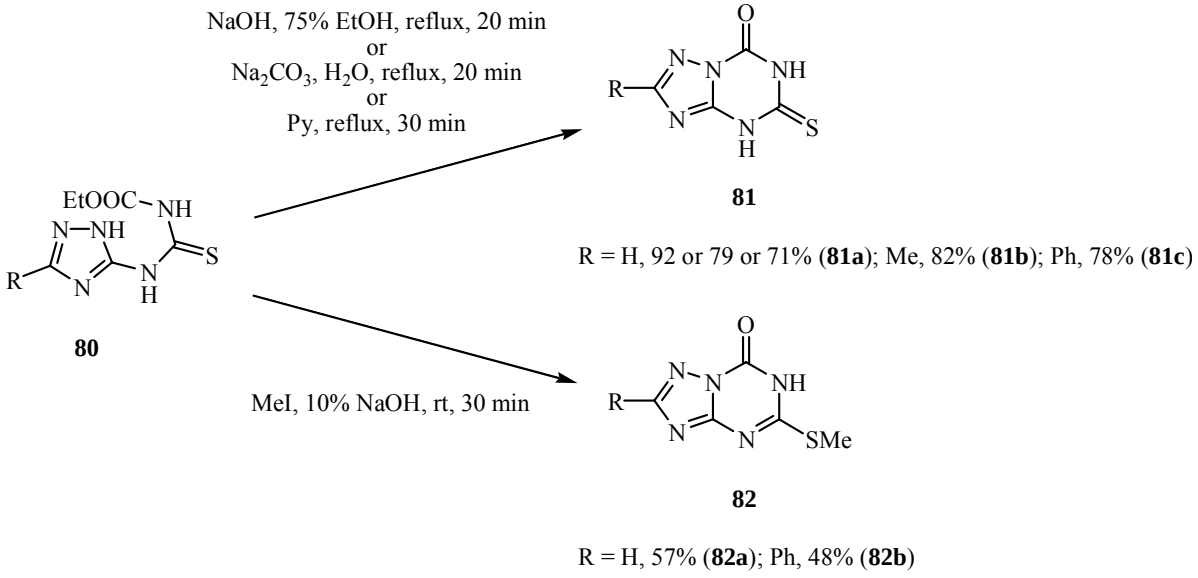
The synthesis of 5,7-dioxo-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (5-azaxanthine, **74**) was found to be successful *via* cyclization of *N*-(1,2,4-triazol-3(5)-yl)-*N'*-carbethoxyurea (**79**) by heating in aqueous solution of sodium carbonate (Scheme 35).[34] Identity of the isolated compound (**74**) with the product prepared form **73** (*vide supra* Scheme 32) confirmed that the cyclization of urea (**79**) proceeded at N1 of the 1,2,4-triazole ring.



79 **74**

Scheme 35

Analogously, *N*-(1,2,4-triazol-3(5)-yl)-*N'*-carbethoxyurea (**80**) were cyclized to 7-oxo-5-thioxo-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**81**).[25,26,34] The corresponding 5-methylthio substituted compounds (**82**) were prepared using iodomethane in aqueous alkali (Scheme 36).[26]



80

81

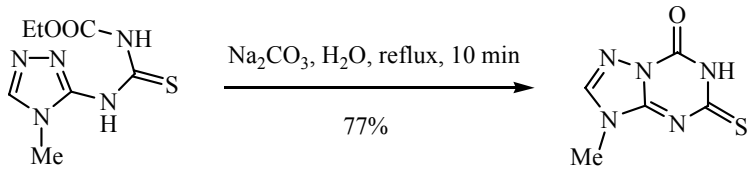
R = H, 92 or 79 or 71% (**81a**); Me, 82% (**81b**); Ph, 78% (**81c**)

82

R = H, 57% (**82a**); Ph, 48% (**82b**)

Scheme 36

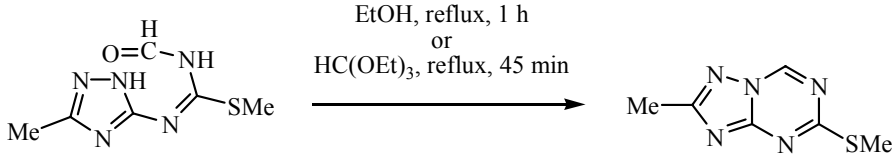
When the similar reactions were attempted using 1- and 4-methyl substituted 1,2,4-triazoles, only 4-methyl substituted triazole (**83**) was found to give the cyclization product – 3-methyl-7-oxo-5-thioxo-[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**84**) (Scheme 37).[26] The authors[26] used this fact and similarity of UV spectra of **80** and **84** to confirm the participation of N1 of **80** in the ring closure.



83 **84**

Scheme 37

It was found that heating of *N'*-formyl substituted isothiourea (**85**) in ethanol or triethyl orthoformate resulted in the heterocyclization with the formation of **68c** (Scheme 38).[50]

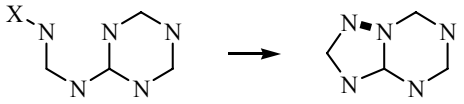


85 **68c**

Scheme 38

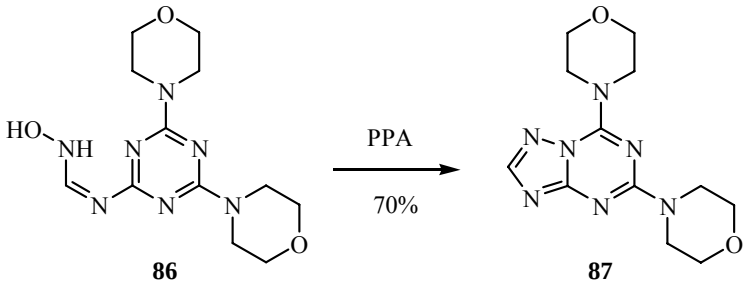
3. ANNULATION OF THE 1,2,4-TRIAZOLE RING ONTO A 1,3,5-TRIAZINE SCAFFOLD

The methods of the preparation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines by annulation of the 1,2,4-triazole ring are limited. The general strategy that was used to construct the 1,2,4-triazole ring involved one-bond formation *via* (5+0) intramolecular heterocyclizations of 1,3,5-triazines having N-C-N-X fragment at C2(4)(6) atom, where X is a leaving group (OH or NH_2) (Scheme 39).



Scheme 39

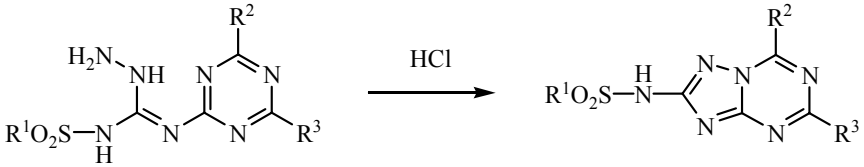
Thus, 5,7-dimorpholyl[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**87**) was synthesized from **86** *via* dehydration upon the treatment with polyphosphoric acid (Scheme 40).[54,55]



86 **87**

Scheme 40

The ring closure deamination of the aminoguanidine derivatives (**88**) was found to proceed in hydrochloric acid and lead to 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**89**) (Scheme 41).[56] The compound (**18h**) with herbicidal activity was prepared in 72% yield using this method. The regioselectivity of the triazole ring annulation in case of unsymmetrical 1,3,5-triazines (**88**, $R^2 \neq R^3$) was not discussed.



88 **89**

Scheme 41

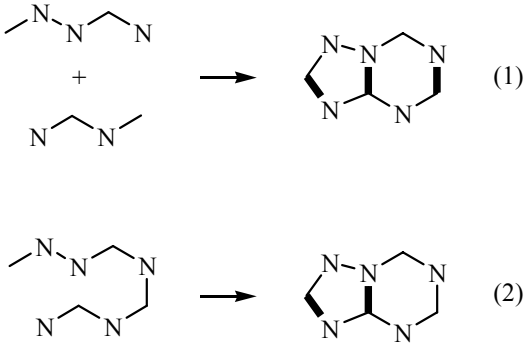
4. CONCURRENT FORMATION OF BOTH THE 1,3,5-TRIAZINE AND 1,2,4-TRIAZOLE RINGS

This synthetic strategy for the preparation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines was developed by Miyamoto[57-59] and may be schematically represented by two groups of reactions (Scheme 42):

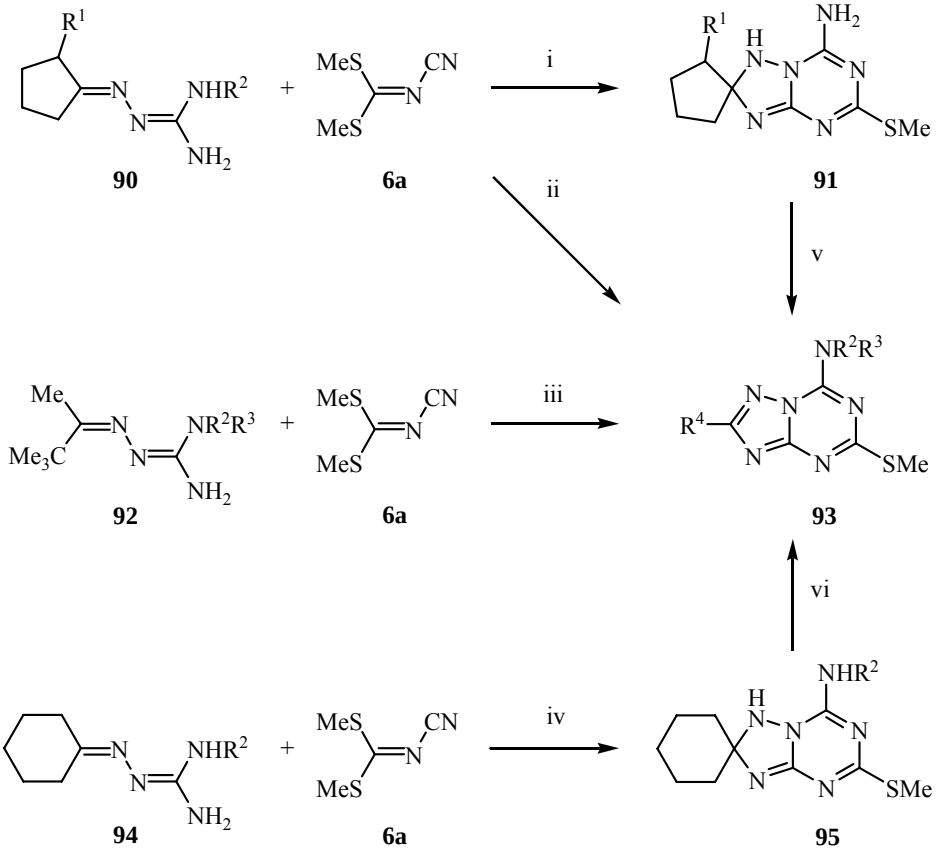
1) Double ring closure comprising three-bound formation by (5+4) atoms heterocyclization using reactions of five-atom fragments consisting of two carbons and three nitrogens (C_2N_3) with four-atom fragment consisting of two carbons and two nitrogens (C_2N_2).

2) Double ring closure comprising two-bound formation by intramolecular heterocyclization of (9+0) atoms open structures consisting of four carbons and five nitrogens (C_4N_5).

In the (5+4) heterocyclizations, diaminomethylenehydrazones provided the C_2N_3 fragment and *N*-cyano substituted imidates (**6a,e**) served as C_2N_2 fragment. Thus, diaminomethylenehydrazones of cyclic ketones (**90**) and (**94**) were found to react with dimethyl *N*-cyanodithiocarbonimidate (**6a**) affording spiro compounds (**91**) and (**95**) (Scheme 43).[57] When diaminomethylenehydrazones of highly hindered ketone (**92**) were used in the reaction with **6a**, spontaneous loss of the *tert*-butyl group with the formation of fully conjugated system (**93**) was observed. Heating of the spiro compounds (**91**) and (**95**) in methanol was found to give the ring-cleaved 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**93**) (Table 7). The prepared compounds were adequately characterized by the spectral analysis data.



Scheme 42



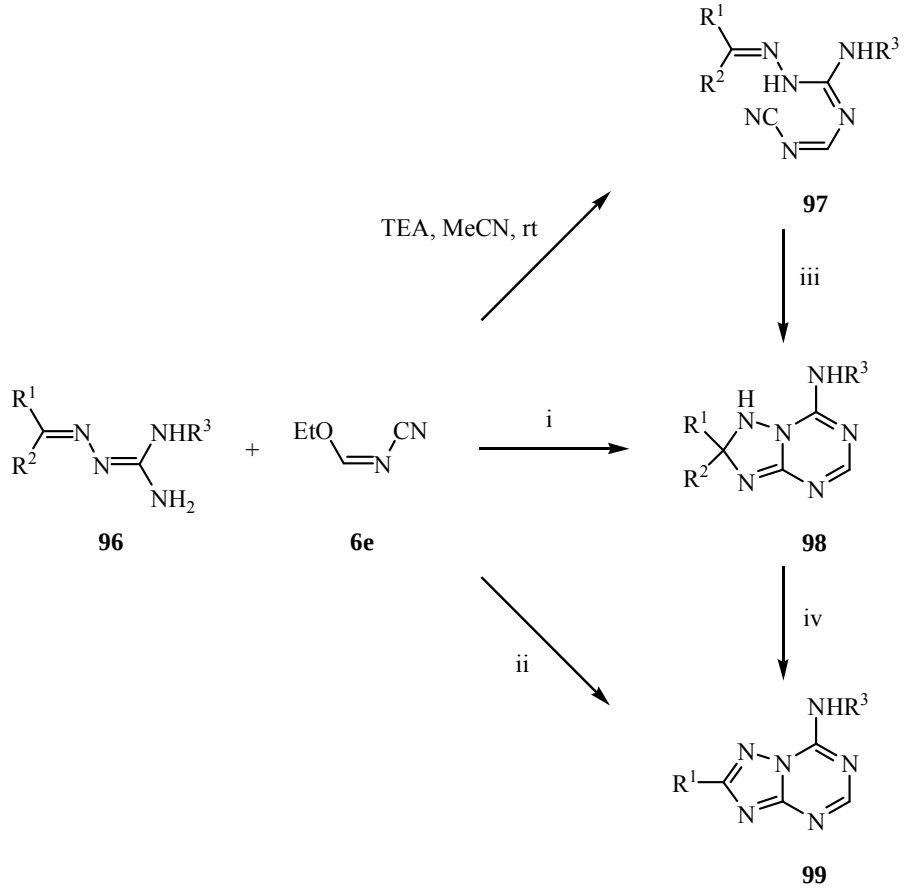
Scheme 43

The reaction of the diaminomethylenehydrazones (**96**) with ethyl *N*-cyanoformimidate (**6e**) gave open-chain products (**97**), 1,2-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**98**) or fully conjugated

7-amino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**99**) (Scheme 44).[57-59] The structure of the products depended on the structure of the starting diaminomethylenehydrazones (**96**) and the reaction conditions (Table 8). The open-chain compounds (**97**) were found to undergo (9+0) intramolecular heterocyclization with formation of 1,2-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**98**) (Scheme 44).

Table 7. Reactions of diaminomethylenehydrazones (**90**, **92** and **94**) with dimethyl *N*-cyanodithiocarbonimidate (**6a**).[57]

Compd.	R^1	R^2	R^3	R^4	Synthetic pathway	Reaction conditions	Yield, %
91a	H	H	-	-	i	MeCN, reflux, 10 min	74
91b	Me	H	-	-	i	MeCN, reflux, 10 min	64
93a	-	H	H	Me	iii	MeCN, reflux, 1 h	92
93b	-	Me	H	Me	iii	MeCN, reflux, 1 h	61
93c	-	Me	Me	Me	iii	MeCN, reflux, 1 h	53
93d	H	H	H	*n*-Bu	v	MeOH, reflux, 1 h	80
93e	H	Me	H	*n*-Bu	ii	MeCN, 55-70 ºC, 1 h	23
93f	H	Me	H	*n*-Pent	v	MeOH, reflux, 1 h	69
93g	Me	Me	H	*n*-Pent	ii	MeCN, 55-70 ºC, 1 h	24
	-	Me	H	*n*-Pent	vi	MeOH, reflux, 1 h	70
95a	-	H	-	-	iv	MeCN, reflux, 10 min	75
95b	-	Me	-	-	iv	MeCN, reflux, 10 min	52



Scheme 44

Table 8. Reactions of diaminomethylenehydrazones (**96**) with ethyl *N*-cyanoformimidate (**6e**).

Compd.	R^1	R^2	R^3	Synthetic pathway	Reaction conditions	Yield, %	Refs.
98a	Ph	H	H	i	TEA, MeCN, reflux, 10 min	48	58, 59
				iii	MeCN, reflux, 1 h	70	58, 59
98b	Ph	Me	H	i	TEA, MeCN, reflux, 10 min	56	58
				iii	MeCN, reflux, 1 h	88	58
98c	C_6H_4Cl-4	H	H	i	TEA, MeCN, reflux, 1 h	60	58, 59
				iii	MeCN, reflux, 1 h	60	59
98d	C_6H_4Cl-4	Me	H	i	TEA, MeCN, reflux, 10 min	51	58
				iii	MeCN, reflux, 1 h	40	58, 59
98e	C_6H_4Br-2	H	H	i	TEA, MeCN, reflux, 10 min	33	58
				iii	MeCN, reflux, 1 h	63	58
98f	C_6H_4OMe-4	H	H	i	TEA, MeOH, reflux	45	59
				iii	MeCN, reflux, 1 h	84	58, 59
98g	C_6H_4OMe-4	Me	H	iii	MeCN, reflux, 1 h	50	58
98h	$C_6H_4NO_2$-4	H	H	i	TEA, MeCN, reflux, 10 min	48	58
				iii	MeCN, reflux, 1 h	40	58
98i	$C_6H_4NO_2$-4	Me	H	i	TEA, MeCN, reflux, 10 min	59	58
				iii	MeCN, reflux, 1 h	79	58
98j	C_6H_3F-2 Cl-4	H	H	iii	MeOH, reflux	nr	59
98k	$(CH_2)_5$		H	i	MeCN, rt, 3 h	44	57
98l	$(CH_2)_5$		Me	i	MeCN, rt, 3 h	10	57
99a	Ph	*i*-Pr	H	ii	TEA, MeOH, rt, 3 h	32	58
99b	C_6H_4Cl-4	H	H	iv	I_2, EtOH, rt, 24 h	33	59
99c	C_6H_4Cl-4	H	Me	ii	MeCN, rt or MeOH, reflux	40-50	59
99d	C_6H_3F-2 Cl-4	H	H	ii	TEA, MeOH, reflux	60	59
				iv	I_2, EtOH, rt, 24 h	nr	59
99e	C_6H_3F-2 Cl-4	H	Me	ii	MeCN, rt	30	59

nr – not reported

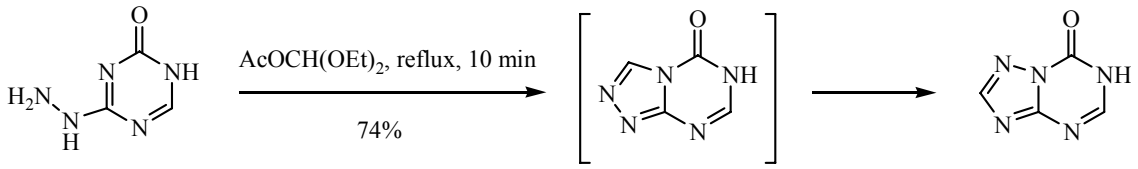
5. SYNTHESES *VIA* RING TRANSFORMATION REACTIONS

The ring transformation reactions used for the syntheses of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines can be rubricated into (1) intramolecular rearrangement of 1,2,4-triazolo[4,3-*a*][1,3,5]triazines to 1,2,4-triazolo[1,5-*a*][1,3,5]triazines and (2) other reactions which mainly consist of the transformations of the cationic 1,3,4-thidiazolo[3,2-*a*][1,3,5]triazines.

5.1. Intramolecular rearrangement of 1,2,4-triazolo[4,3-*a*][1,3,5]triazines to 1,2,4-triazolo-[1,5-*a*][1,3,5]triazines.

It was predicted that the thermodynamically less stable 1,2,4-triazolo[4,3-*a*][1,3,5]triazines should rearrange to their thermodynamically more stable [1,5-*a*] fused isomers *via* Dimroth rearrangement.[60] The 2(4)(6)-hydrazino substituted 1,3,5-triazines and their derivatives were used for the preparation of required 1,2,4-triazolo[4,3-*a*][1,3,5]triazines. However, the isolation of the relatively unstable [4,3-*a*] intermediates was not always possible due to the isomerization which took place at the reaction conditions and resulted in the formation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines.

When 4-hydrazino substituted 1,3,5-trazin-2-one (**100**) was heated under reflux with diethoxymethyl acetate, 7-oxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**44a**) (5-azahypoxanthine) was obtained (Scheme 45).[61] It was evident that the reaction pathway involved the formation of 1,2,4-triazolo[4,3-*a*][1,3,5]triazine (**101**) as an intermediate which further rearranged to **44a**.

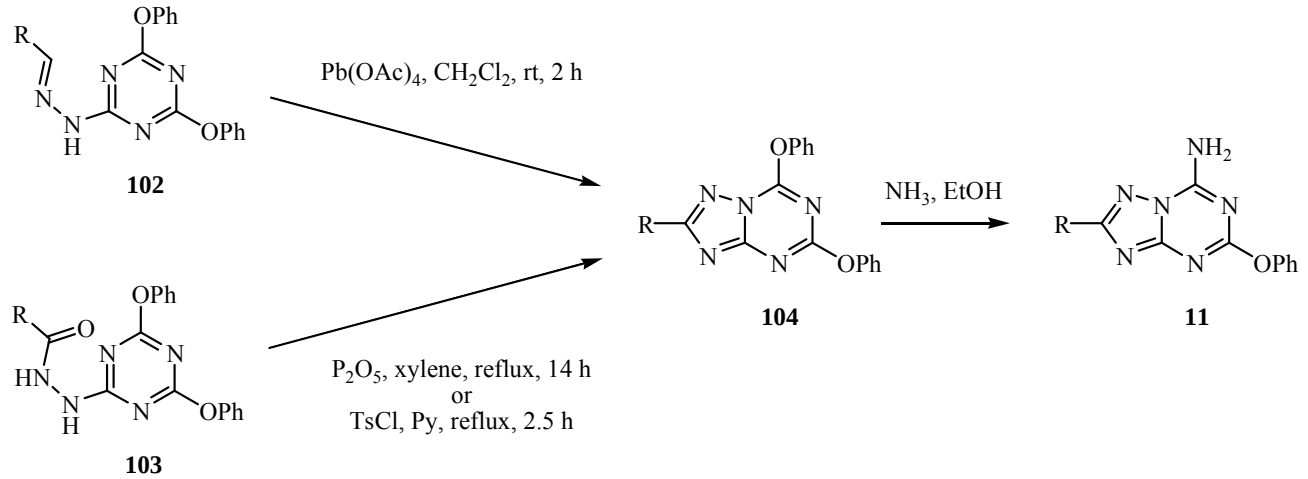


100 **101** **44a**

Scheme 45

Without isolation of the intermediate 1,2,4-triazolo[4,3-*a*][1,3,5]triazines, 5,7-diphenoxy[1,2,4]triazolo-[1,5-*a*][1,3,5]triazines (**104**) were synthesized by oxidative cyclization of hydrazones (**102**) with lead tetracetate or dehydration of hydrazides (**103**) (Scheme 46).[7] The spectral and elemental analysis data were given only for 5,7-diphenoxy[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**104**, R=2-furyl), other compounds were converted to their 7-amino derivateves (**11a**) prior the characterization.

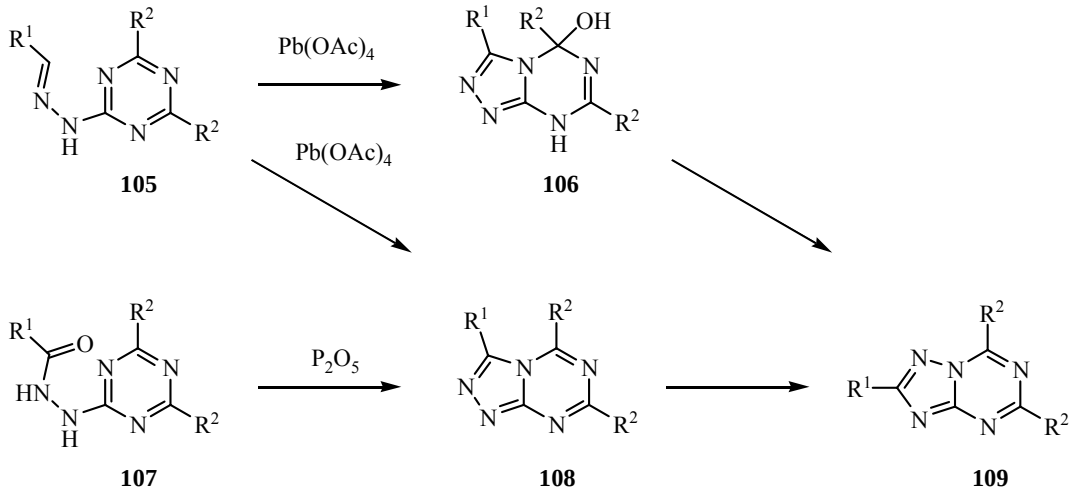
It was found that 5,7-diphenoxy[1,2,4]triazolo[4,3-*a*][1,3,5]triazines (**104**) could be prepared from hydrazides (**103**) in substantially improved yield using a polyphosphoric acid silyl ester as a dehydrating agent.[62] This method was used for the synthesis of selective A_{2a} antagonist ZD 9255 (*vide infra*).[11] The compounds (**104**) were claimed to be intermediates for biologically active compounds.[62]



102 **103** **104** **11**

Scheme 46

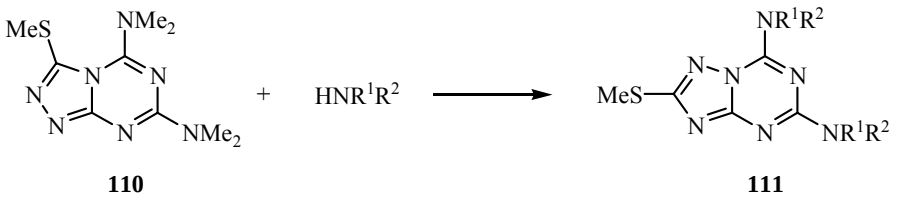
The isolation of the intermediate 5,7-diamino substituted 1,2,4-triazolo[4,3-*a*][1,3,5]triazines (**108**) in similar reactions was described (Scheme 47).[63-65] The products (**108**) readily underwent a thermal rearrangement above their melting points. The isomerization of 1,2,4-triazolo[4,3-*a*][1,3,5]triazines (**108**) to the [1,5-*a*] fused isomers (**109**) was also effected by treating the compounds (**108**) with aqueous or methanolic alkali solution (Table 9). Interestingly, the oxidation of the hydrazone (**105**, $R^1 = C_6H_4NO_2$-2, R^2 = morpholyl) afforded the hydrated dihydro intermediate (**106**) which also may undergo the rearrangement with lost of water molecule and formation of the corresponding 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**109o**).[64]



Scheme 47

The reaction of 5,7-bis(dimethylamino)-3-methylthio[1,2,4]triazolo[4,3-*a*][1,3,5]triazine (**110**) with amines was found to afford the rearrangement products (**111**) in which dimethylamino group at position 7 was replaced by the reactant amine (Scheme 48).[66]

The compound (**110**) was also reported to undergo the acid catalyzed rearrangement. The heating of aqueous solution of the hydroiodide salt of **110** at 110 ºC for 16 h gave (after neutralization) 15:85 mixture of **110** and **111a** in 53% yield.[66] The results of X-ray crystallographic study for **111a** were reported.[67]



Scheme 48

The rearrangement of 1,2,4-triazolo[4,3-*a*][1,3,5]triazines fused with pyrazole ring to 1,2,4-triazolo[1,5-*a*][1,3,5]triazine derivatives was described. Thus, when tricyclic compound (**112**) was heated at its melting point, the isomer with [1,5-*a*] junction of the triazole and triazine rings was formed

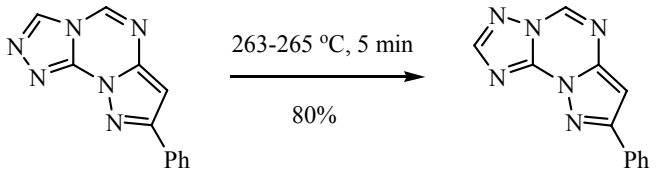
(Scheme 49).[68,69] The reaction of the compound (**114**) with hydrazine involved the isomerization with formation of the [1,5-*a*] fused derivative (**115**) (Scheme 50).[68,70]

Table 9. Rearrangement of 1,2,4-triazolo[4,3-*a*][1,3,5]triazines (**106** and **108**) to 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**109**).

Compd.	R^1	R^2	Reagents and reaction conditions	Yield, %	Refs.
109a	H	NMe_2	2% NaOH, MeOH, rt, 2 h	50-60	63
109b	Me	NMe_2	2% NaOH, MeOH, rt, 2 h	50-60	63
109c	Me	piperidyl	2% NaOH, MeOH, rt, 2 h	50-60	63
109d	Me	morpholyl	2% NaOH, MeOH, rt, 2 h	50-60	63
109e	Ph	NMe_2	2% NaOH, MeOH, rt, 2 h	50-60	63
109f	Ph	NMe_2	5% NaOH, MeOH, reflux, 1 h	85	64
109g	Ph	piperidyl	2% NaOH, MeOH, rt, 2 h	50-60	63
109h	Ph	morpholyl	2% NaOH, MeOH, rt, 2 h	50-60	63
109i	C_6H_4Cl-2	NMe_2	5% NaOH, MeOH, reflux, 1 h	87	64
109j	C_6H_4Cl-3	NMe_2	5% NaOH, MeOH, reflux, 1 h	90	64
109k	C_6H_4Cl-4	NMe_2	5% NaOH, MeOH, reflux, 1 h	85	64
109l	C_6H_4Cl-4	piperidyl	235-240 ºC, 1.5 h	65	65
109m	C_6H_4OMe-4	morpholyl	240-245 ºC, 15 min	30	65
109n	$C_6H_4NO_2$-2	NMe_2	5% NaOH, MeOH, reflux, 1 h	94	64
109o	$C_6H_4NO_2$-2	morpholyl	5%, NaOH, MeOH, reflux, 1 h	85	64
109p	$C_6H_4NO_2$-3	NMe_2	5% NaOH, MeOH, reflux, 1 h	70	64
109q	$C_6H_4NO_2$-4	NMe_2	5% NaOH, MeOH, reflux, 1 h	70	64
109r	$C_6H_3Cl_2$-2,6	piperidyl	230 ºC, 10 h	31	65
109s	$C_6H_4(OMe)_2$-3,4	piperidyl	215-220 ºC, 0.5 h	50	65

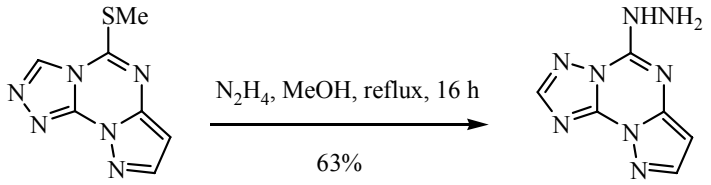
Table 10. Reaction of 5,7-bis(dimethylamino)-3-methylthio[1,2,4]triazolo[4,3-*a*][1,3,5]triazine (**110**) with amines.[66]

Compd.	R^1	R^2	Reaction conditions	Yield, %
111a	H	Ph	EtOH, reflux, 24.5 h	53
111b	Me	Me	EtOH, 85 ºC, sealed tube, 6.25 h	88
111c		$(CH_2)_4$	EtOH, reflux, 8 h	77



112 **113**

Scheme 49

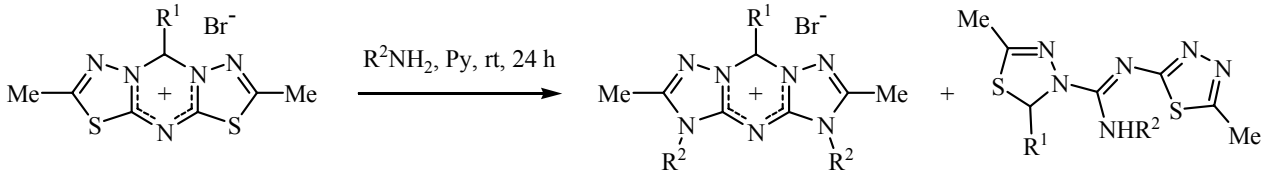


114 **115**

Scheme 50

5.2. Other ring transformations.

The reactions of di[1,3,4]thidiazolo[3,2-*a*:3',2'-*d*][1,3,5]triazinium bromides (**116**) with two equivalents of benzylamines or their pyridyl analogues at ambient temperature were found to afford separable mixtures of the compounds (**117**) and (**118**) (Scheme 51).[71] Di[1,2,4]triazolo[1,5-*a*:5',1'-*d*][1,3,5]-triazinium bromides (**118**) were formed *via* the rupture of the 1,3,4-thidiazole rings of **116** and subsequent recyclization together with desulfurization. The mechanism of this ring transformation reaction was explained using experimental data and B3LYP/6-311++G(d,p) calculations as S_N (ANRORC) process accompanied by intramolecular proton-transfer reactions.[71] The prepared compounds (**117**) were fully characterized using spectral analysis data and results of X-ray crystal structure determination for **117a**.



116 **117** **118**

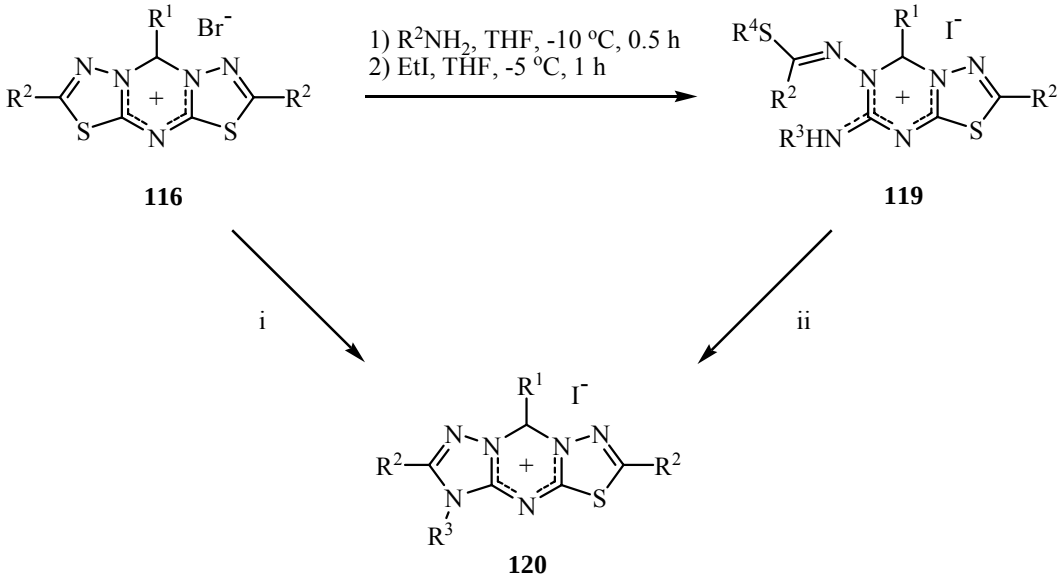
Scheme 51

Table 11. Reaction of di[1,3,4]thidiazolo[3,2-*a*:3',2'-*d*][1,3,5]triazinium bromides (**116**) with benzylamines.[71]

Compd.	R^1	R^2	Ratio **117/118**	Yield, %*
117/118a	*n*-Bu	CH_2Ph	50:50	80
117/118b	C_6H_4Me-4	CH_2Ph	46:54	61
117/118c	C_6H_4Me-4	$CH_2C_6H_4Cl$-2	60:40	74
117/118d	C_6H_4Me-4	$CH_2C_6H_4Cl$-4	58:42	67
117/118e	C_6H_4Me-4	$CH_2C_6H_4OMe$-2	13:87	78
117/118f	C_6H_4Me-4	$CH_2C_6H_4Me$-4	35:65	86
117/118g	C_6H_4Me-4	CH_2Py-2	62:38	33
117/118h	C_6H_4Me-4	CH_2Py-4	47:53	61
117/118i	1-Naph	CH_2Ph	50:50	64

The aminolysis of di[1,3,4]thidiazolo[3,2-*a*:3',2'-*d*][1,3,5]triazinium bromides (**116**) was carried out at low temperature and followed by reaction with alkyl iodide (Scheme 52).[71,72] The temperature regime at the second step of the reaction (Table 12) determined the formation of the bicyclic (**119**) or tricyclic (**120**)

iodides. The synthesis of **120** was achieved *via* desulfurization of **119** accompanied by ring closure. The structure of the compounds (**120**) was confirmed using spectroscopic methods and X-ray crystallography for **120g**.



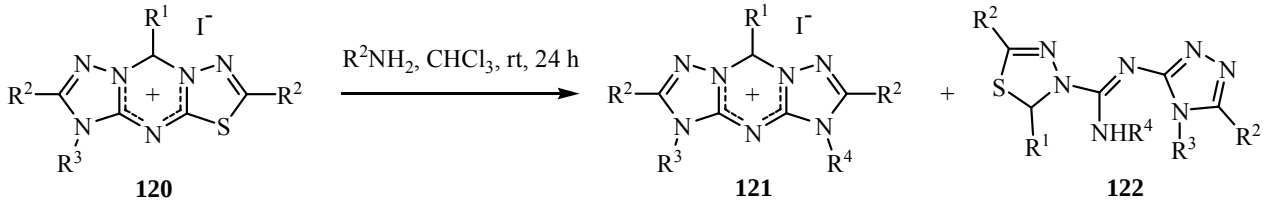
Scheme 52

Table 12. Synthesis of 1,3,4-thiadiazolo[3,2-*a*][1,2,4]triazolo[5,1-*d*][1,3,5]triazinium iodides (**120**).

Compd.	R^1	R^2	R^3	Synthetic pathway	Reagents and reaction conditions	Yield, %	Refs.
120a	C_6H_4OH-2	Et	*n*-Bu	i	1) R^2NH_2, THF, -10 ºC, 0.5 h; 2) MeI, -10 ºC, 0.5 h, 70-80 ºC, 7 h	92	72
120b	C_6H_4OH-2	Et	CH_2Ph	i	1) R^2NH_2, THF, -10 ºC, 0.5 h; 2) MeI, -10 ºC, 0.5 h, 70-80 ºC, 7 h	79	72
120c	C_6H_4OH-2	*t*-Bu	CH_2CH_2Py-2	ii	Py, reflux, 5 h	98	71
120d	C_6H_4OH-2	*t*-Bu	$CH_2CH_2C_4H_3S$-2	ii	Py, reflux, 5 h	98	71
120e	C_6H_4Me-4	Me	CH_2Ph	i	1) R^2NH_2, THF, -10 ºC, 0.5 h; 2) EtI, rt, 5 h, 50 ºC, 1 h	70	71
120f	C_6H_4Me-4	Me	$CH_2C_6H_4Cl$-4	i	1) R^2NH_2, THF, -10 ºC, 0.5 h; 2) MeI, -10 ºC, 0.5 h, 70-80 ºC, 7 h	98	72
120g	C_6H_4Me-4	Me	$CH_2C_6H_4OMe$-2	i	1) R^2NH_2, THF, -10 ºC, 0.5 h; 2) EtI, rt, 5 h, 50 ºC, 1 h	84	71
120h	1-Naph	Me	$CH_2C_6H_4Cl$-4	i	1) R^2NH_2, THF, -10 ºC, 0.5 h; 2) MeI, -10 ºC, 0.5 h, 70-80 ºC, 7 h	91	72

The 1,3,4-thiadiazolo[3,2-*a*][1,2,4]triazolo[5,1-*d*][1,3,5]triazinium iodides (**120**) were found to have further synthetic applications in the preparation of other interesting 1,2,4-triazolo[1,5-*a*][1,3,5]triazine derivatives. When 1,3,4-thiadiazolo[3,2-*a*][1,2,4]triazolo[5,1-*d*][1,3,5]triazinium iodides (**120**) were

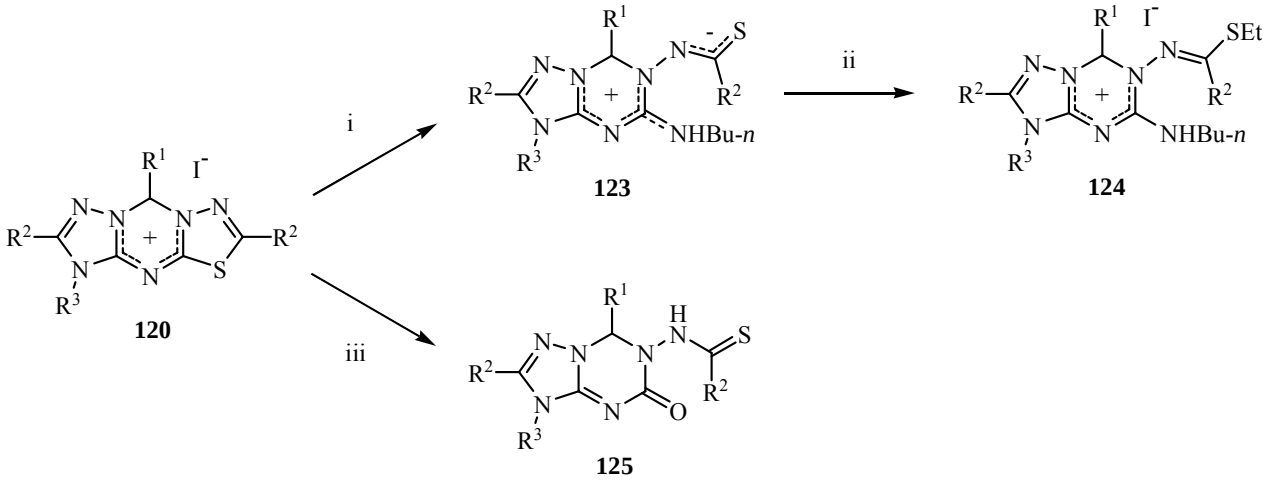
allowed to react with primary amines, polysubstituted di[1,3,4]thidiazolo[3,2-*a*:3',2'-*d*][1,3,5]triazinium iodides (**121**) were formed together with products of 1,3,5-triazine ring cleavage (**122**) (Scheme 53).[72]



120 **121** **122**

Scheme 53

The reaction of **120** with *n*-butylamine at relatively low temperature was found to result in the formation of the stable mezoionic compounds (**123**) which were further underwent *S*-alkylation to give 1,2,4-triazolo[1,5-*a*][1,3,5]triazinium iodides (**124**) (Scheme 54).[72] When after treatment of **120** with amines the reaction mixture was acidified using acetic acid, the hydrolysis products **125** were formed. The structures of the prepared compounds were established using spectroscopic data and X-Ray crystallography results for **123a** and **125a**.



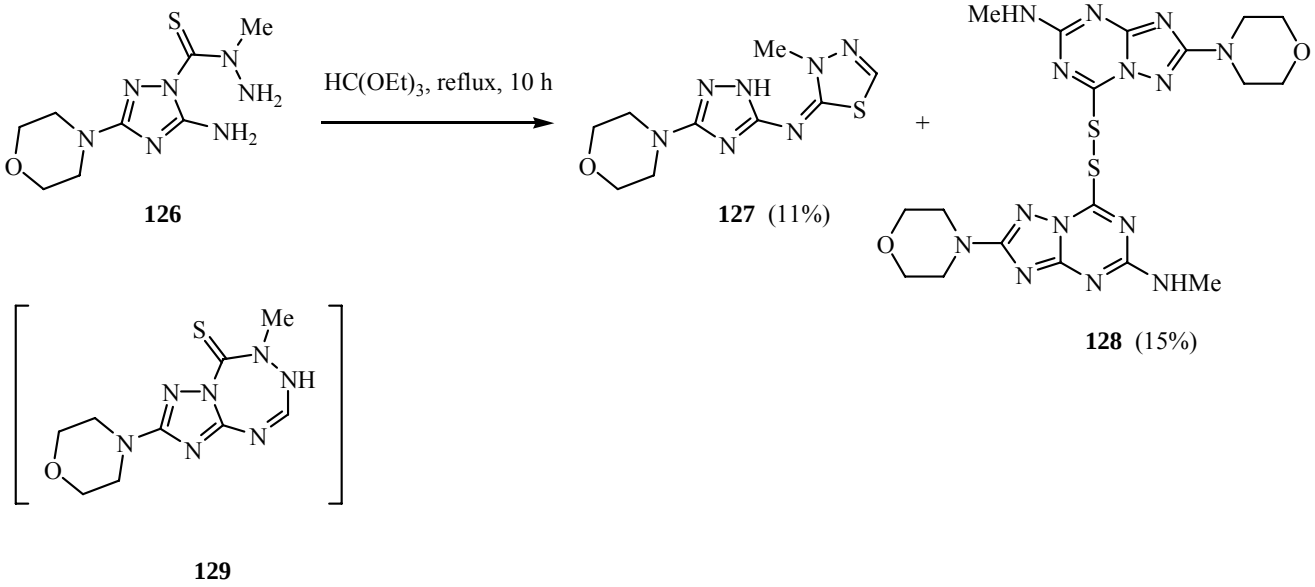
120 **123** **124** **125**

Scheme 54

Table 13. Reactions of [1,3,4]thiadiazolo[3,2-*a*][1,2,4]triazolo[5,1-*d*][1,3,5]triazinium iodides (**120**).[72]

Compd.	R^1	R^2	R^3	Synthetic pathway	Reagents and reaction conditions	Yield, %
123a	C_6H_4Me-4	Me	CH_2Ph	i	*n*-$BuNH_2$, TEA, $CHCl_3$, -10-5 ºC, 3 h	90
123b	C_6H_4Me-4	Me	$CH_2C_6H_4Cl$-4	i	*n*-$BuNH_2$, TEA, $CHCl_3$, -10-5 ºC, 3 h	79
123c	C_6H_4OH-2	Et	*n*-Bu	i	*n*-$BuNH_2$, TEA, $CHCl_3$, -10-5 ºC, 3 h	98
123d	1-Naph	Me	$CH_2C_6H_4Cl$-4	i	*n*-$BuNH_2$, TEA, MeCN, -10-5 ºC, 3 h	86
124a	C_6H_4Me-4	Me	CH_2Ph	ii	EtI, THF, 5 ºC, 1 h	66
124b	C_6H_4Me-4	Me	$CH_2C_6H_4Cl$-4	ii	EtI, THF, 5 ºC, 1 h	65
124c	1-Naph	Me	$CH_2C_6H_4Cl$-4	ii	EtI, THF, 5 ºC, 1 h	90
125a	C_6H_4Me-4	Me	CH_2Ph	iii	1) *n*-$BuNH_2$, TEA, rt, 24 h; 2) AcOH, pH 6-7	93
125b	C_6H_4Me-4	Me	$CH_2C_6H_4Cl$-4	iii	1) *n*-$BuNH_2$, TEA, rt, 24 h; 2) AcOH, pH 6-7	86

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**128**) was found to be formed as one of the products of the reaction of the substituted 1,2,4-triazole (**126**) with ethyl orthoformate. The proposed mechanism of the reaction involves the rearrangement of the intermediate (**129**).[73]



126 **127** (11%) **128** (15%)

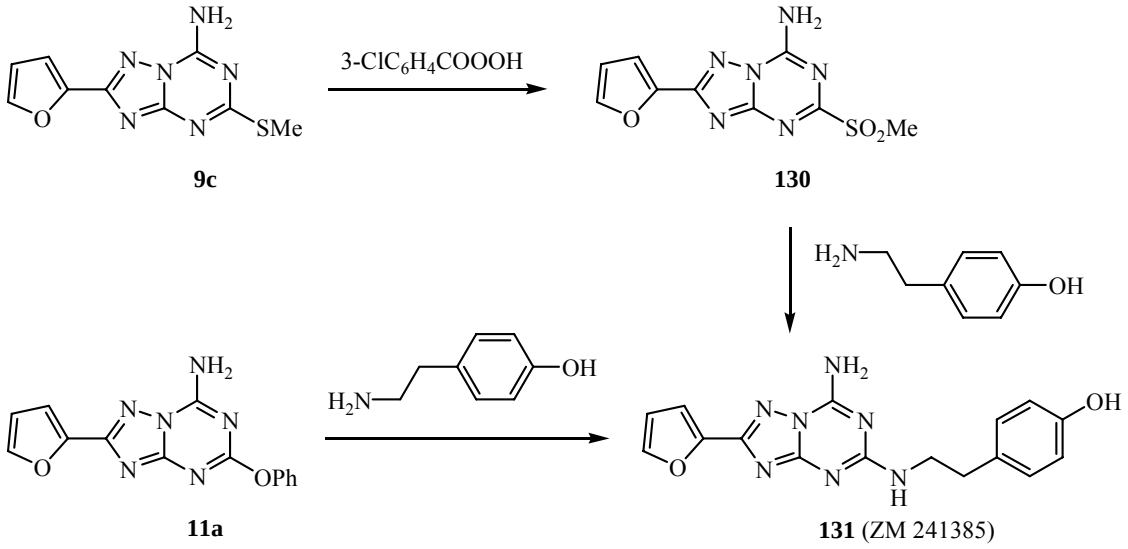
129

Scheme 55

6. BIOLOGICAL ACTIVITY OF 1,2,4-TRIAZOLO[1,5-*a*][1,3,5]TRIAZINE DERIVATIVES

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazine derivatives were screened against a variety of biological targets with particular attention devoted to the inhibition of adenosine receptors. Since the first report[10] in 1991, the 1,2,4-triazolo[1,5-*a*][1,3,5]triazines were recognized as selective nonxanthine inhibitors of A_{2a} type of adenosine receptors. The A_{2a} adenosine receptors are widely expressed in the central nervous system and are attractive drug targets. The inhibitors of A_{2a} adenosine receptors may be used in the treatment of various neurological disorders such as Parkinson's disease, depression, anxiety, and cerebrovascular disorders, which are associated with the A_{2a} receptor signaling pathways.

From comparative studies[74,75] of nonxanthine-based inhibitors of the A_{2a} receptors that have different types of heterocyclic skeleton, it was identified that compounds having 1,2,4-triazolo[1,5-*a*][1,3,5]triazine as the core structure afforded inhibitors with the best A_{2a} receptor binding affinity. It was found that 2-furyl substituent at position 2 as well as the amino group at position 7 of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus are crucial for the inhibitory activity. Variations of the substituents at position 5 of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazines were investigated in an attempt to improve the affinity, selectivity and bioavailability of the compounds. The most active compounds were identified among the derivatives as those with substituted amino group at position 5. Two approaches to the synthesis of this type of compounds based on the nucleophilic substitution of **11a** or the sulphone (**130**) prepared from **9c** with substituted amines.[7-12,62,74-81] It may be illustrated with the synthesis of the inhibitor o ZM 241385 (**131**) (Scheme 56).



Scheme 56

The compound (**131**, ZM 241385) was found to possess high affinity and selectivity to A_{2a} adenosine receptors (Table 14) and therefore it became widely used as a standard reference compound. The detail information on the pharmacology of ZM 241385 (**131**) has been reported in the literature.[82-85]

The modifications of substituents at position 5 of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazines identified that the inclusion of a piperazine spacer at this position improved oral bioavailability of the compounds. Thus, compounds (**132**) and (**133**) demonsterated good results in the radioligand binding assays (Figure 4, Table 14) and this was translated to significant activity at 3 mg/kg (p.o.) in the animal Parkinson's disease models.[76,77] The compound (**134**) with flexible linker between the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus and piperazine ring was found to have good activity and selectivity towards A_{2a} receptors in both the radioligand binding and animal model assays.[78]

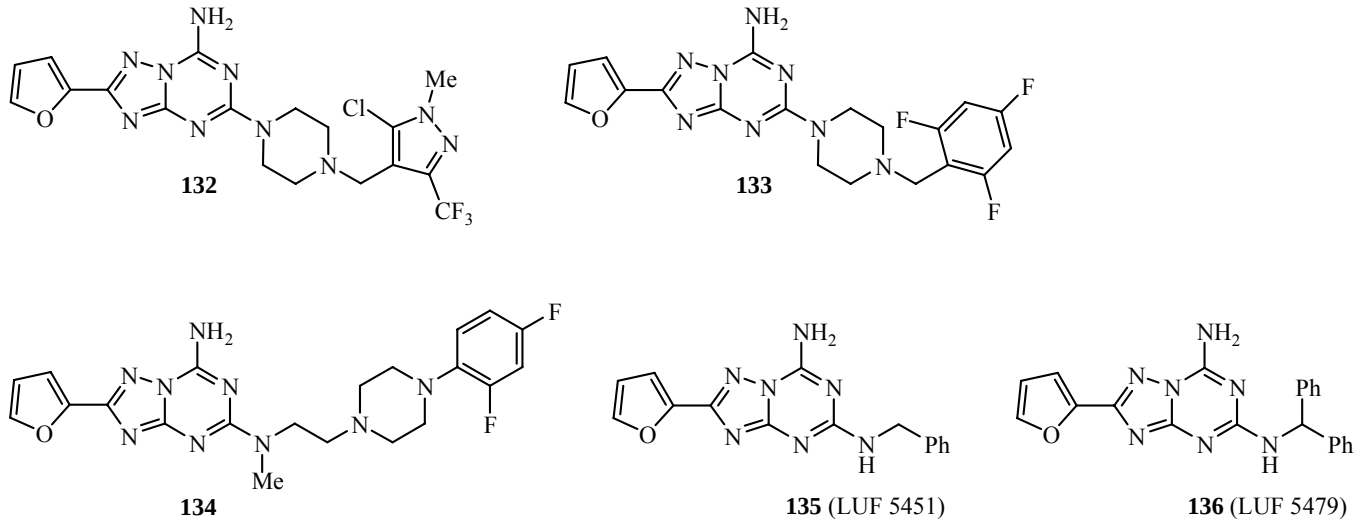


Figure 4

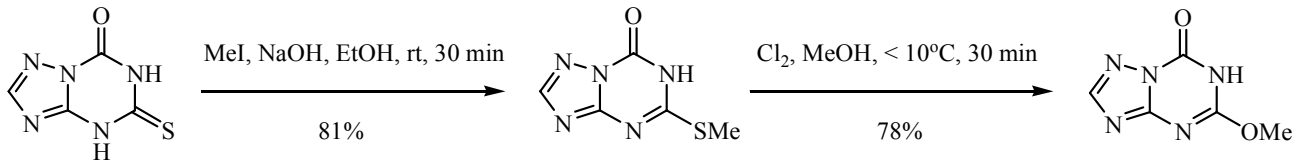
Table 14. The affinity of some 1,2,4-triazolo[1,5-*a*][1,3,5]triazines to different types of adenosine receptors in the radioligand binding assays.

Compd.	A_1 K_i, nM	A_{2a} K_i, nM	A_{2b} K_i, nM	A_3 K_i, nM	Refs.
131	680	0.9	-	-	76,77
	257	1.78	16.5	3090	79
	255	0.8	-	> 10000	82
132	1100	14	-	-	76
133	1300	3	-	-	77
134	820	4	-	-	78
135	13	13	7.6	207	79
136	3.6	35.9	> 10000	22.3	79

Most of the 7-amino-2-(2-furyl)-1,2,4-triazolo[1,5-*a*][1,3,5]triazines were found to be selective inhibitors against the A_{2a} adenosine receptors. However, the selectivity of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazines towards the different types of adenosine receptors may change dramatically with variations of the substituents at position 5. Thus, the addition of the second phenyl ring at the α-position of the benzylamino substituent of relatively selective inhibitor of the A_{2b} adenosine receptors LUF 5451 (**135**), transformed it into rather selective A_1 receptor inhibitor LUF 5479 (**136**) with the lost of A_{2b} affinity.[79]

It should be noted that **11b** with phenoxy group at position 5 was claimed to be useful for the treatment of depression[86] and Parkinson's disease.[87] The mechanism of the effects may be also associated with the inhibition of adenosine receptors.

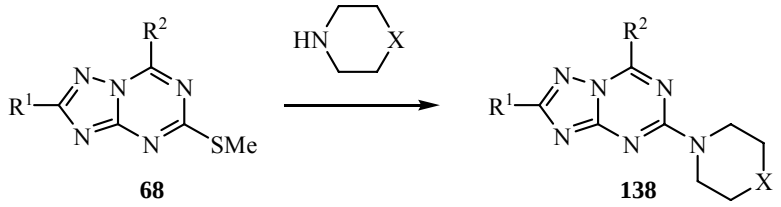
It was found that the 7-oxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazine derivatives structurally related to xanthine inhibited xanthine oxidase.[35] 5-Azaxanthine (**74**) and its 5-thioxo analogue (**81a**) inhibited the enzyme with IC_{50} value of 45 and 100 μM, respectively. The methylation of these compounds changed the activity dramatically. The xanthine oxidase inhibitory activity of 5-methylthio-7-oxo[1,2,4]triazolo-[1,5-*a*][1,3,5]triazine (**82a**) prepared *via* methylation of **81a** (Scheme 57) was higher than that of the well-known drug allopurinol (IC_{50} value of 1.4 *vs* 5.9 μM). The 5-methoxy substituted **137**, synthesized from **82a** showed IC_{50} value of 80 μM.



81a **82a** **137**

Scheme 57

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**138**) prepared upon the treatment of **68** with cyclic amines (Scheme 58) were claimed[24] to be potent bronchodilators.

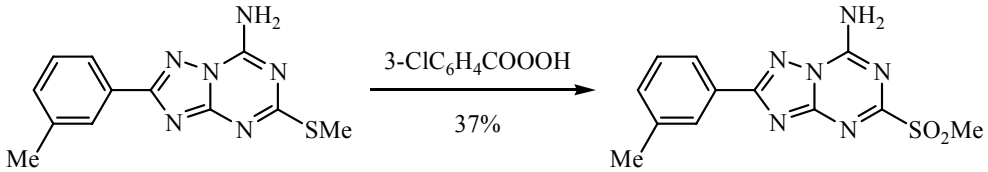


68 **138**

R^1 = H, Me, Et, Ph; R^2 = Me, Et; X = CH_2, O, S, NMe

Scheme 58

The sulfone (**139**) synthesized by oxidation of **9b** (Scheme 59) was claimed[6] to possess properties useful in the therapy of the diseases associated with inflammation.



9b **139**

Scheme 59

In the search of new agents for treatment of immune-related diseases, in particular, immunosuppressants,[5,88] a number of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines was screened at the different models of eosinophilia and the 7-thioxo substituted compound (**47h**) was found to be able to inhibit eosinophilia at as low a dose as 0.3 mg/kg, p.o.

The 5,7-diaryl substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**18c,d,f,g**) were tested for their anticancer and antioxidant activities.[16] The highest antiproliferation and antioxidant potential was found in **18f**. This compound (**18f**) was further evaluated against 60 human cancer cell lines and demonstrated the high growth inhibition against renal cancer cell line A498 (IC_{50} value of 0.49 μM).

The antibacterial and antifungal activities of a number of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines with (thi)oxo groups at positions 5 and 7 (**63**, **64** and **66**) were evaluated.[47-49] The level of the observed activity was not encouraging; in general, more pronounced antifungal activity was found for **64**.[48]

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazines were reported to possess properties useful in agriculture. Thus, in the screening of the compounds with phytotoxic activity, the compounds (**98c,j**) and (**99b-d**) were found to suppress cell growth and chlorophyll formation of green microalgae *Scenedesmus acutus*.[59] The 5,7-dioxo[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**25**) were claimed[22] to be herbicides, *e.g.* the compound (**25**, R^1 = R^2 = *i*-Pr) at 1 kg/ha post-emergence gave complete control of *Stellaria media*. The 2-sulfonylamino substituted 1,2,4-triazolo[1,5-*a*]1,3,5-triazines (**89**)[17,18,56] and 6,7-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazines (**42**)[32] were also found to be useful as herbicides.

7. CONCLUSION

A variety of the effective methods for the preparation of 1,2,4-triazolo[1,5-*a*]1,3,5-triazines has been reported, mainly *via* the annulation of the 1,3,5-triazine ring onto a 1,2,4-triazole scaffold. The

1,2,4-triazolo[1,5-*a*]1,3,5-triazines have been utilized as suitable skeletons for the design of biologically active compounds, ranging from pesticides to agents with good therapeutical potential.

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